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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

INTERNATIONAL RECORD OF CLINICAL AND RESEARCH PSYCHIATRY

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The *Journal of Clinical and Experimental Psychopathology* was founded in 1939 by V. C. Branham, M.D., as the *Journal of Criminal Psychopathology*. In 1944 the title was changed to the *Journal of Clinical Psychopathology*; in 1951 the journal became the *Journal of Clinical and Experimental Psychopathology*. The present title (*Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology*) was assumed in 1954.

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SUPPLEMENT 1
APRIL–JUNE 1958

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EDITORIAL

Toward a Unifying Concept in Psychiatry

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THE VAN OPHUIJSEN CENTER
NEW YORK, N. Y.

"We are today on the threshold of the era of metabolic medicine and metabolic psychiatry. . . . Through the metabolic era psychiatry will come to its fullest understanding of neuronal physiology and its relationship to psychodynamics."[1]

"It is our hope that those who have made such fine contributions in different sectors will dedicate some of their time to unifying concepts that will not only relate critical elements of the work on serotonin and norepinephrine to the findings on psychomimetic and psychotherapeutic agents but that [our approach] will be broadened so as to encompass the great body of neuroendocrine and clinical data. . . . Let us not . . . perpetrate . . . a dichotomy

and divorce chemistry of the brain from physiology of the body as a whole and from the neuroendocrine system in particular, or from other elements of either the internal or external milieu. We must unify a wide body of observations. . . . The door between laboratory and clinic must never be closed and different laboratories must be connected by conceptual bridges. . . . The historic advances in neuroendocrine and biochemical research in psychiatry today demand a unifying concept."[2]

Today, eight years following the first statement, and less than one year following the second, we are participating in a common endeavor that may mark a beginning of a fulfillment of what had been presented as a prophecy and as a hope. In this symposium the chemist and the psychiatrist, the rheumatologist and the cardiologist, the investigator in cancer and in geriatrics join hands. This was inevitable. For those of us in psychiatry who have long felt that one could not divorce the psyche from the brain and thinking from the neuron, this is a welcome event. Our data and studies have long indicated the inevitability of a metabolic definition of the etiology and the pathogenesis of psychiatric as well as related psychosomatic and neuroendocrine disorders.[3,4]

There was a time when we presented psychiatric reports at a physiologic congress or hematologic data at a psychiatric convention and evoked many a quizzical expression and look of bewilderment. Yet, one cannot probe any pathophysiology deeply without ultimately reaching tissue metabolic processes. The psychiatrist investigating a new psychotherapeutic agent, the rheumatologist investigating a new antirheumatic compound, and the cardiologist investigating a new anti-hypertensive and anti-angina pectoris drug, in the most natural course of events meet at the cellular metabolic level. Today, in what superficially appears to be a matter of course, but what is in reality a historic occasion, we witness an inter-disciplinary meeting of the greatest significance.

This symposium has resulted in the presentation of a large body of preliminary data, some of it excellent and some of it open to debate; part of it definitive and part premature. This is only natural. The leads that have been turned up in the investigation of monoamine oxidase inhibitors are so vital that it is good to have early as well as frequent interchange of findings and opinions.

The material of this symposium holds vital leads and lessons not only for psychiatry, but for chemistry in general, for enzymology more particularly, and for clinical medicine in several fields. This symposium is the earliest fruit of interdisciplinary thinking in a basic metabolic area and therefore thinking more broadly than in terms of psychiatry or any one branch of medicine—and we hope this fruit will in turn provide the seed for the theoretical concepts that will enable us to integrate better the different disciplines participating here. We are personally fascinated by the fact that a single chemical agent is influ-

encing at different and yet related clinical levels a psychiatric disorder, a skeletal disease, and a cardiovascular dysfunction. For us, this is the fulfillment of a theoretical approach, which on hypothetical grounds based on earlier data suggested that such conditions could be interrelated.[3,4]

There is much evidence to suggest that the rapidly accelerating advances in therapeutics are about to receive further impetus as we explore these new leads that relate so vitally to the basic enzyme systems fundamental to cellular metabolism. We must press forward with boldness in our vision, in our theory, and in our investigations but with caution in our practical applications. We are dealing here with very basic functions and when we are so fortunate as to be able to influence fundamental processes, our responsibilities grow in proportion to the extent of our ability. The greater the measure with which our new therapeutic instruments influence physiologic processes, the greater our responsibility in their application. We have learned at this symposium of important therapeutic potentials, but if we are to see their greatest and happiest fulfillment, we must simultaneously recognize that these agents *must* be used with understanding of their potency because they have potentials for harm as well as for help. An agent that can truly and effectively influence a basic body parameter may theoretically influence that parameter to a point which is viewed, in common terminology, as "toxicity." Since iproniazid is actively affecting a fundamental enzyme system, excessive dosages may have negative therapeutic implications. A number of investigators have experienced and reported both minor and major side effects of sufficient import to urge caution in therapeutic application and to suggest the need for meticulous observation of the patient receiving monoamine oxidase inhibitors. It is therefore an obligation of investigators to define more precisely the true limits of therapeutic benefit and of therapeutic restrictions and to clarify dosage ranges in various conditions and under varying circumstances. It is obligatory upon physicians using these agents to be aware constantly of both the desirable and undesirable potentials.

This symposium should provide medicine with two new opportunities: First, and most significantly, the opportunity for the creation of unifying concepts that will clarify our understanding of a number of critical psychiatric, cardiovascular, and endocrinologic states, and, second, in the field of practical therapeutics, it can point the way to using more advanced weapons for medicine's attack upon three of the most vital sectors of man's well-being—common psychiatric states, chronic rheumatologic disorders, and all too common cardiovascular conditions.

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SYMPOSIUM ON THE BIOCHEMICAL AND CLINICAL ASPECTS OF MARSILID AND OTHER MONOAMINE OXIDASE INHIBITORS*

The History of Marsilid

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NUTLEY, NEW JERSEY

The main purpose of this symposium is to bring together and coordinate our knowledge of Marsilid.‡ Since there are so many facets to the study and the use of Marsilid, a preliminary history of its discovery and development may help to coordinate our thinking.

In 1951, Dr. H. H. Fox of the Hoffmann-La Roche Laboratories, was working on the synthesis of new compounds for the treatment of tuberculosis. In an attempt to synthesize a pyridine analogue of the German compound tibione, isonicotinic acid hydrazide was derived as an intermediate in the synthesis. This intermediate was tested against tuberculosis in mice by Drs. Schnitzer and Grunberg at the Hoffmann-La Roche Laboratories and in clinical tuberculosis by Drs. Robitzek, Selikoff, and Ornstein of Sea View Hospital. It was found effective in both mice and men. This compound is now commonly known as isoniazid and has provided the parent structure for a large number of variants. One of these variants is 1-isonicotinyl, 2-isopropyl hydrazine, the generic name of which is iproniazid, and the trade name of which is Marsilid (fig. 1).

Historically it is significant that both iproniazid (Marsilid) and isoniazid§ were developed by the same men in the same series of experiments and for the same condition, and that both compounds were discussed in the early publications in this field. This, and the fact that the words iproniazid and isoniazid are so similar, has led to much confusion. I shall, therefore, refer to iproniazid as Marsilid hereafter.

In their first published papers, Drs. Selikoff, Robitzek, and Ornstein stated that "central nervous stimulation is apparently also to be listed among the side effects." Since this was more marked with Marsilid in the doses used for tuberculosis and since it was considered an undesirable side effect, isoniazid was given preference and came into wide use for tuberculosis, whereas Marsilid was nearly abandoned. Dr. David Bosworth continued to use Marsilid and clearly stated that it had valuable properties over and above its effect on

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* Papers presented herein were read initially at a meeting sponsored by Hoffmann-La Roche, Inc., on November 29 and 30, 1957, in New York, New York.

† Department of Clinical Investigation, Hoffmann-La Roche, Inc.

‡ Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

§ The trade name of Hoffmann-La Roche, Inc. for isoniazid is Rimifon.

tuberculosis. In 1955 he pointed out that Marsilid helped the patient in general and the healing process in particular. Nevertheless, the drug might have been forgotten as an agent for human therapy had it not been for three groups of workers who, quite independently and almost simultaneously, studied the effect of Marsilid on mental depressions. These were Dr. Nathan Kline with Drs. Loomer and Saunders at the Rockland State Hospital, Dr. Crane at the Montefiore Hospital, and Dr. Scherbel with Drs. Schuchter and Harrison at the Cleveland Clinic and Hospital.

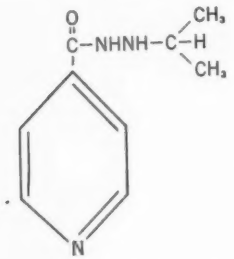

FIG. 1. 1-Isonicotinyl-2-isopropyl hydrazine (Marsilid).

On April 6, 1957, at the regional meeting of the American Psychiatric Association held in Syracuse, Dr. Kline reported on the results of treatment of severely depressed and regressed hospitalized psychotic patients with Marsilid. Although not all the patients were improved, and in some cases the improvement came very slowly, the point was made that Marsilid had helped some chronically depressed patients who had not been helped by any other therapy. At the same meeting, Dr. Crane reported on the use of Marsilid in depressed patients, most of whom had been hospitalized for tuberculosis. Again not all patients were improved and some had undesirable reactions, but it was clear that Dr. Crane also found the treatment improved the mood of some depressed patients. Dr. Scherbel discussed these papers and pointed out that the depression, exhaustion, and anxiety, which accompany chronic disease, may limit the patients' recovery. He and his co-workers had found Marsilid of particular value in treating patients with rheumatoid arthritis who were depressed. Following this meeting Marsilid began to be used widely for the treatment of depressions.

While the clinical studies were leading to widespread interest in Marsilid, laboratory studies were leading to important knowledge concerning the possible mode of action of the drug. In 1952, Dr. Zeller and his co-workers in Chicago found that Marsilid was an inhibitor of monoamine oxidase. Since then, its effects on at least ten more enzymes have been reported, but the effect of Marsilid on monoamine oxidase appears to be the most significant.

The particular importance of monoamine oxidase in mental function became clearer after it was established that serotonin in the brain was converted by the enzyme to the excretion product 5-hydroxyindole acetic acid. The formation and metabolism of serotonin was also studied by Dr. Udenfriend and his collaborators at the National Heart Institute.

These workers found that, when Marsilid was given to animals, it produced a rapid and large rise in the level of brain serotonin.

Work done in Dr. Brodie's laboratory at the National Heart Institute had shown that reserpine caused a release of serotonin from brain, blood platelets, and intestines. Drs. Brodie, Shore, and Pletscher studied a number of compounds known to have central action for their ability to release serotonin. This ability "was limited to *Rauwolfia* alkaloids and, of these, to the alkaloids that exert tranquilizing effects." The information that Marsilid, an energizer, was able to raise the level of serotonin in the brain and that reserpine, a tranquilizer, lowered serotonin in brain tissue stimulated much interest in the biochemistry of brain function. The extensive clinical trials with Marsilid have generally confirmed the work of the three groups who reported their preliminary findings in April 1957 and who have extended our knowledge. In a few cases, the therapeutic effect of Marsilid in depressed patients has been almost miraculous. In many cases it has been valuable, but in other cases it has proved of little help. As adjunctive therapy for patients with an emotional component of a chronic disease it has already been found valuable, particularly in rheumatoid arthritis and other collagen diseases, in far advanced cancer, and in acne. Unexpected uses are appearing; Dr. Cesarman's important discovery that Marsilid relieves angina pectoris is an example. The deliberate attempt to induce what was called a side effect has led to encouraging results in the treatment of hypertension. This was shown by Dr. Nussbaum, Dr. Harnes, and others. Marsilid seems to be a drug with many uses.

Along with encouraging therapeutic results came reports of undesirable effects and unanswered questions. One set of undesirable effects was essentially the same as had been reported in 1952 by Drs. Selikoff, Robitzek, and Ornstein and consisted of overstimulation of both mental and physical activity. These should probably be called overdosage effects, as they consist of the many signs and symptoms connected with relative overactivity of what Hess called the ergotropic system of the brain. Reduction in dosage seems to be indicated in these instances. The second set of undesirable effects consisted of potentiation of other drugs such as desoxyephedrine, or prolongation of the action of drugs such as barbiturates. Such results are of course understandable, since it is probably true that most catecholamines are normally broken down by monoamine oxidase. The third type of undesirable reaction consisted of hepatitis, that is, a hepatocellular type of liver damage that is difficult or impossible to distinguish from viral hepatitis. The cause of this is not clear. Fortunately the condition is rare, but it is under intensive study, and physicians must be warned of the possibility. Administration of Marsilid should be stopped in such cases as these.

The questions have been numerous—far too numerous to repeat here. One of the most important concerns the dosage of Marsilid.* Another concerns the time necessary to obtain a response to Marsilid, and whether amphetamine, tryptophan, or other agents should be used with it as a booster. These and other questions have been raised.

* As is true of all potent modern drugs, iproniazid (Marsilid) should be used with full awareness of its potency and of the need for accurate dosage adjustment. Physicians should familiarize themselves with up-to-date literature provided by the manufacturer before prescribing the drug.

It is our sincere hope that this first symposium on Marsilid will be fruitful not only for those of us in attendance, but for the medical profession in its entirety, and for the many thousands who are victims of disorders yet unsolved.

RESUME

Le Marsilid a été découvert en 1951 par le Dr. H. H. Fox de la Compagnie Hoffmann-La Roche. Comme le Marsilid (iproniazide) est chimiquement apparenté à l'isoniazide, il a été initialement utilisé dans le traitement de la tuberculose. Toutefois, la dose préconisée de 300 mg. par jour a provoqué de nombreux effets secondaires et l'usage de la drogue a été abandonné.

Peu après le rapport initial sur l'emploi du Marsilid en tuberculose, le Dr. Bosworth a signalé que le Marsilid accroissait la sensation de bien être et facilitait la cicatrisation dans les cas orthopédiques s'accompagnant de lésions tuberculeuses et non tuberculeuses. L'intérêt suscité par le Marsilid a été encore amplifié lorsque trois groupes indépendants d'investigateurs (Kline, Saunders et Loomer; Crane et Scherbel, Schuchter et Harrison) ont signalé, presque simultanément, la valeur particulière du Marsilid dans le traitement de la dépression et des maladies chroniques accompagnées de troubles émotionnels. Ces cliniciens observèrent que la fréquence et la gravité des réactions secondaires pouvaient être réduites par l'emploi du Marsilid à dose plus faible.

Le Dr. Davis mentionne brièvement les études expérimentales, qui ont procuré d'importantes informations sur le mode d'action possible du Marsilid, et il signale certaines des réactions secondaires que l'on peut observer quand la drogue est utilisée.

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Discussion of the History of Marsilid

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NEW YORK, NEW YORK

At the outset I must say that I am indeed thrilled at the widespread clinical and laboratory investigation that is now under way dealing with the mode of action and the effects of Marsilid. It was not too long ago that I thought this valuable drug was to be removed from the armamentarium. It caused me much distress, for I believed that Marsilid was not only effective in treating various infections, but also that it helped the patient in general and the healing process in particular. At that time I tried to convince Hoffmann-La Roche to continue production of a drug that seemed extremely valuable. Fortunately they agreed to continue production of Marsilid, and fortunately a number of men became interested in evaluating and investigating this drug. As a surgeon I was somewhat limited in my own investigation, but I had the advantage of a good patient population. The examples of the effectiveness of the drug, which I will demonstrate, represent only a small segment of the cases treated. I have selected the early cases, as these have been followed for from four to five years.

Since the clinical value of a drug is the essence of its worth, I am sure that these few examples should provide some measure of the value of Marsilid.

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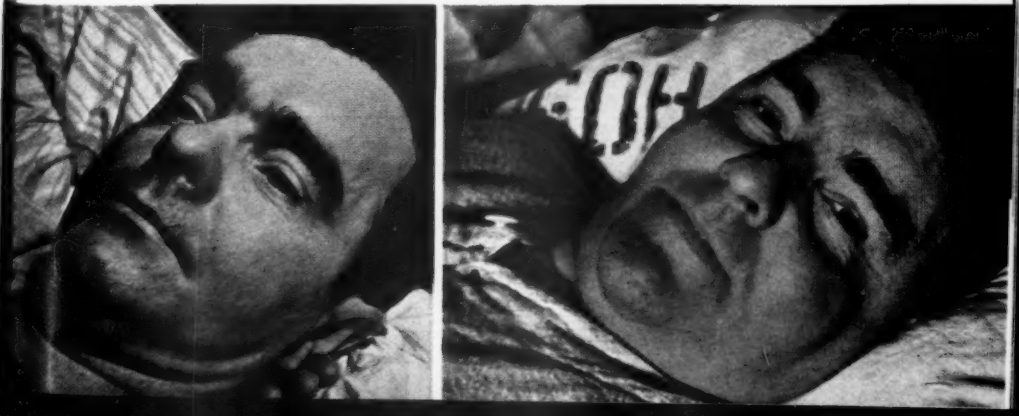
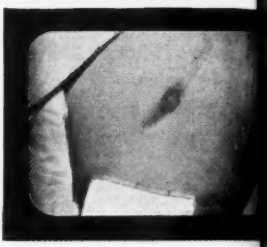
rsilid halts the course of disease and the severe depression in persons with tuberculosis.

This patient with tuberculosis of the hip had been treated for an extended period with streptomycin. Sinuses developed and the patient suffered marked weight loss and severe depression. Administration of Marsilid was finally begun. In a few weeks weight gain and a change in the patient's disposition occurred. He became cooperative and content. The progress of the disease was halted, and the patient's general condition was amazingly improved. Sinuses healed.



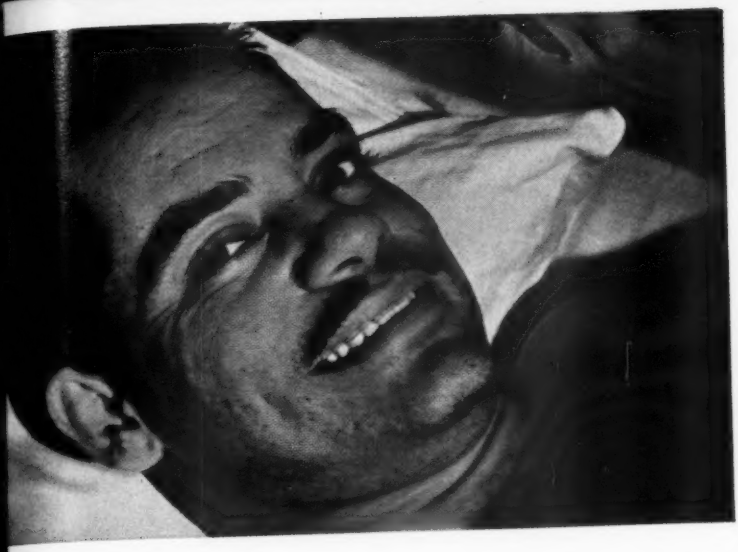


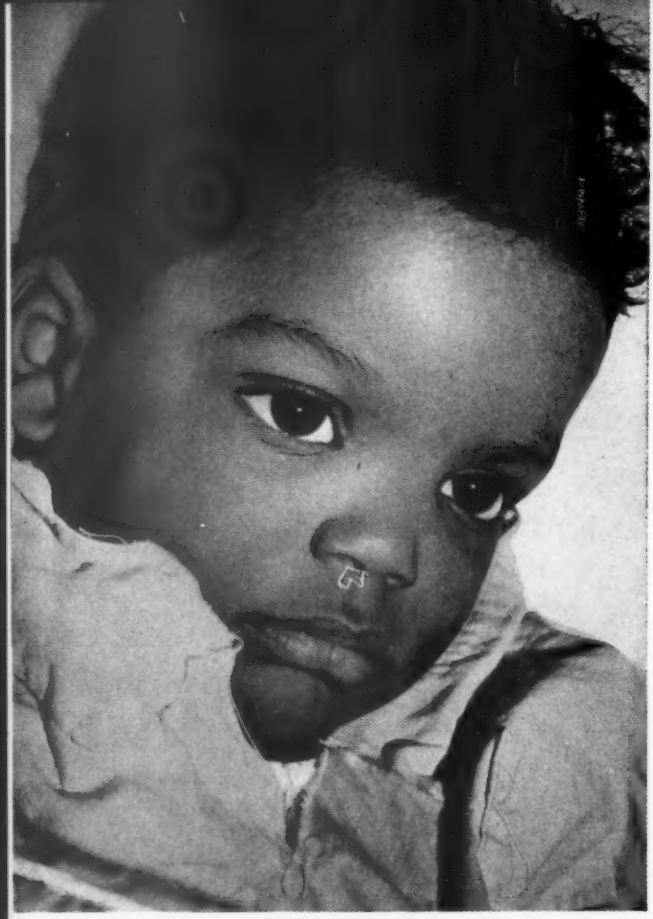
A feeling of well-being, weight gain, and healing of tuberculous sinus results with the use of Marsilid.

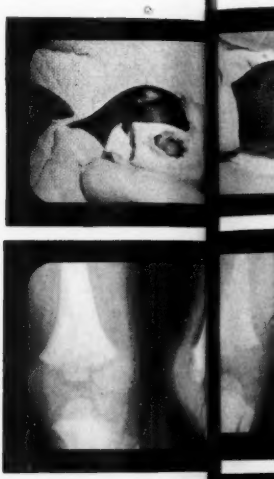
This patient with tuberculosis of the spine had been treated by spinal fusion. The lesion failed to heal and draining sinuses developed. There was no response to streptomycin and the course was progressively downhill. Administration of Marsilid was begun, and the sinuses cleared and healed completely. The patient showed a marked weight gain and a feeling of well-being. The tuberculous sinus tracts of 63 per cent of the patients were healed, and these results were considered excellent.

Resistant tuberculosis of the skin responds to Marsilid.

Previous results in treating persons with tuberculosis of the skin had been poor. This patient with tuberculosis of the skin showed no response to four months of intensive therapy with streptomycin. After receiving Marsilid for four weeks (3 mg./Kg.), healing was complete.

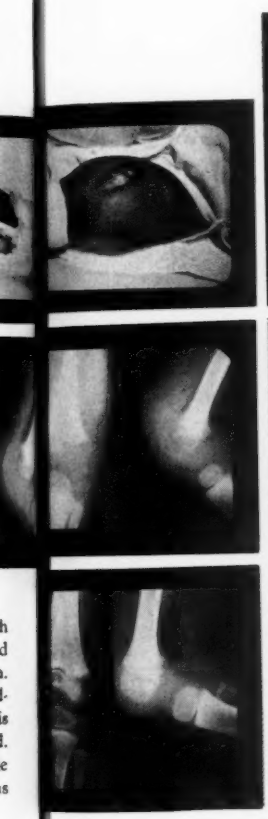


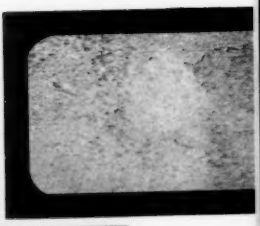


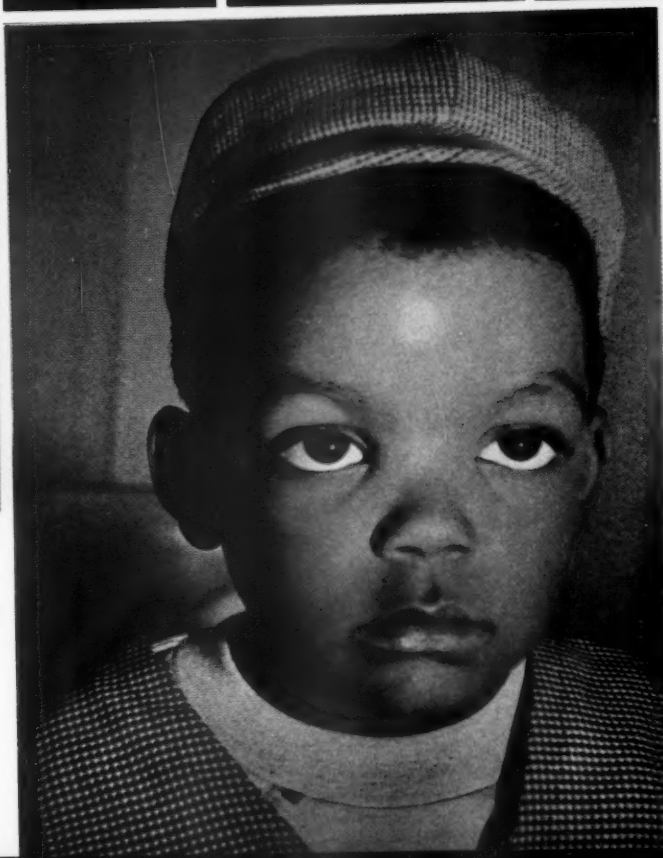


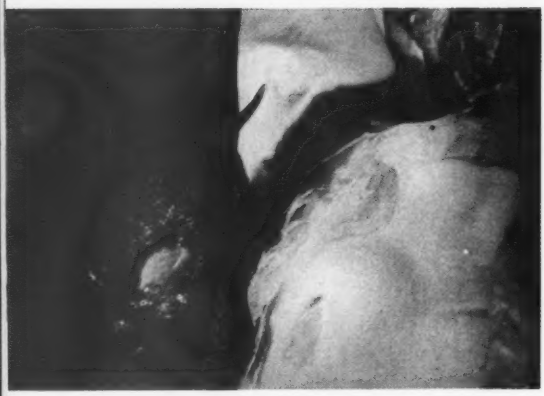
Rehabilitation of young persons occurs with Marsilid therapy.

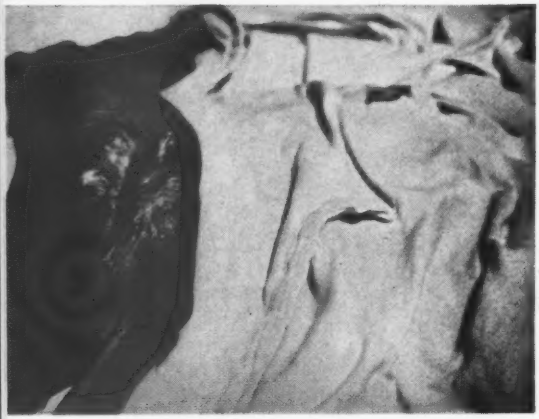
This infant with tuberculosis of the knee, which was proved by histologic examination, showed marked swelling, pain, and limitation of motion. There was no response to streptomycin. With administration of Marsilid (3 mg./Kg.), tuberculosis was controlled and mobility of the joint was restored. The epiphyseal center of the lateral femoral condyle was absorbed and then reformed. The child has made an excellent recovery.









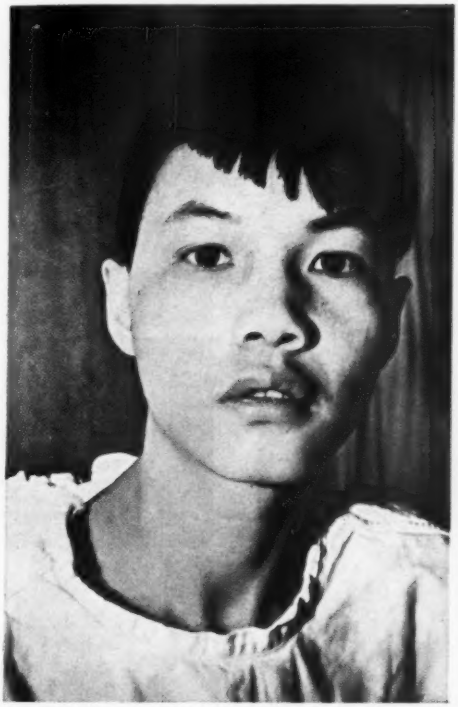


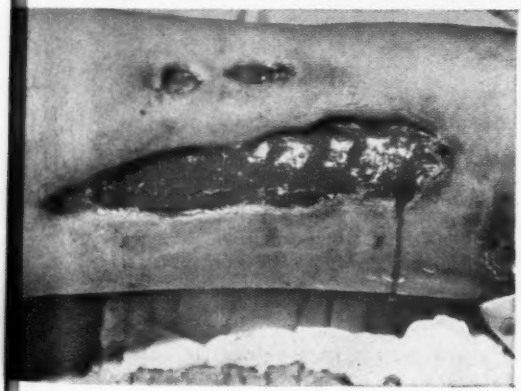
Dramatic changes occur in the preterminal tuberculosis patient.

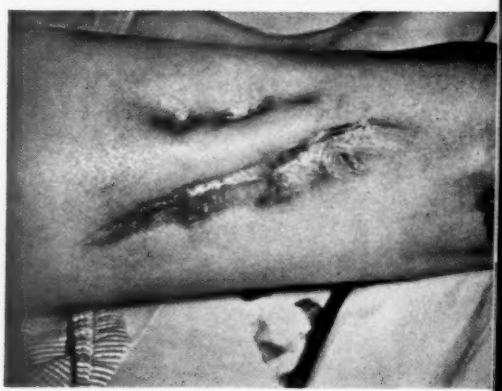
This patient had pulmonary tuberculosis with widespread bone and joint dissemination. Although treated with over 1000 Gm. of streptomycin, he showed no improvement. Administration of Marsilid was finally begun when the patient was in the preterminal stage. In seven weeks six of eight lesions showed evidence of healing. Unfortunately the disease was too far advanced and, in spite of dramatic changes in the lesions, the patient died.

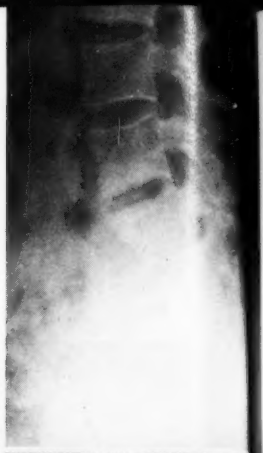
Marsilid causes improvement in the emotional status and the physical well-being of the person who has tuberculosis of the fascia.

In this patient with tuberculosis of the fascia, which has always been difficult to treat, streptomycin was given for eight months and no healing resulted. The wound continued to drain, and patient's general condition was poor. Treatment with Marsilid resulted in marked weight gain and complete healing in four months.



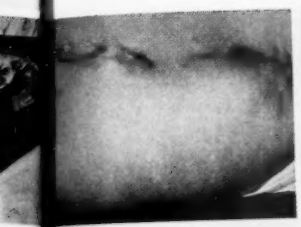


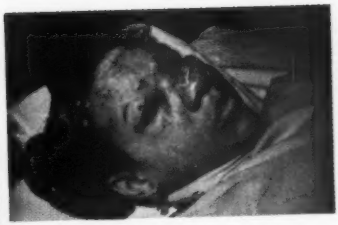


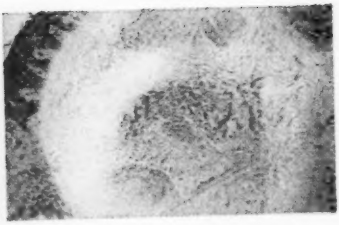


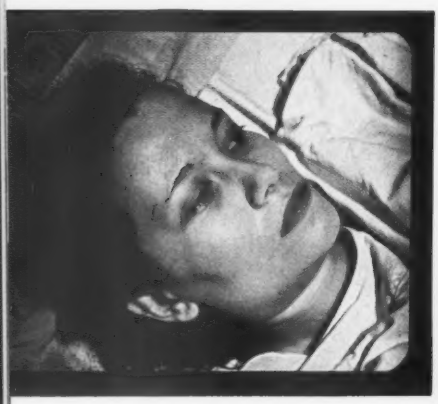
Encouraging progress occurs in the personality and the physical condition of the patient in whom tuberculosis and lupus erythematosis have been proved to exist.

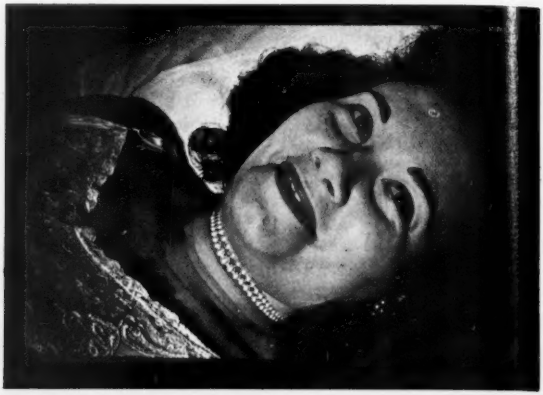
In this patient who had tuberculosis of the spine in 1951, a psoas abscess developed that broke through into the thigh. As a result, the fascia of the thigh was involved and a great deal of sloughing was noted. The patient was treated with streptomycin but no improvement was demonstrated. After six weeks of receiving Marsilid, the tuberculous lesion healed. The patient was also known to have lupus erythematosis. Considerable kidney damage was noted on histologic examination. The patient suffered a great deal of pain. The disease was widely disseminated. Administration of Marsilid was continued, and marked improvement was noted from month to month. Skin lesions healed, and there was a weight gain of 51 pounds. She is alive and well.

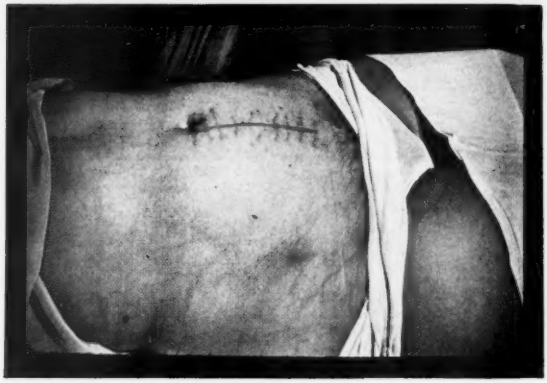










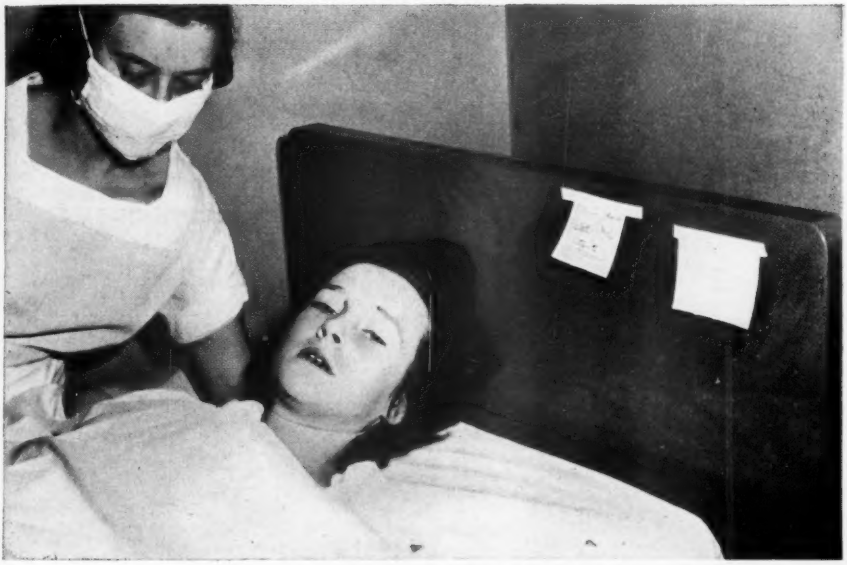


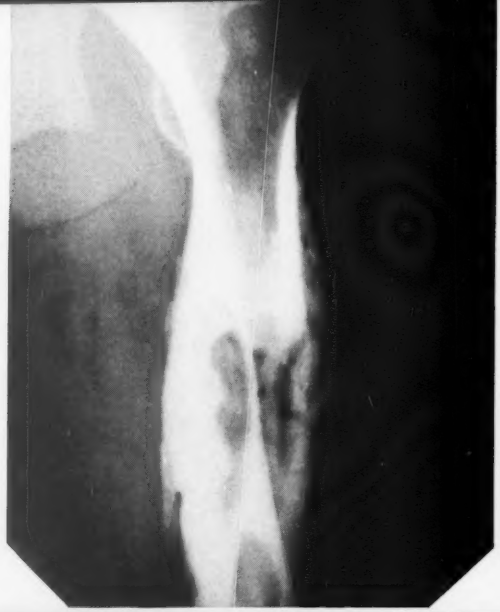
The withdrawn, acutely ill patient with tuberculous peritonitis shows remarkable response to Marsilid.

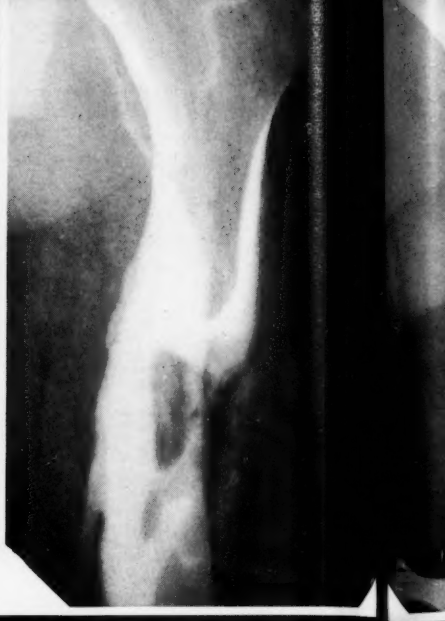
This patient with proved tuberculous peritonitis was seen following abdominal section. She had a high fever and was acutely ill. After treatment with Marsilid her temperature was reduced from 105 to normal in three days. In a four week period, she gained 15 pounds. She is now well and shows no evidence of adhesions.

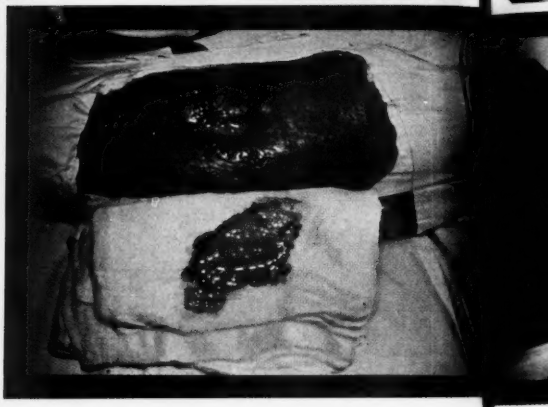
Marsilid is credited with complete recovery and dramatic emotional improvement in patients with tuberculous meningitis.

In persons with tuberculous meningitis amazing results have been noted. This patient was desperately ill. The diagnosis of tuberculous meningitis was proved by spinal tap. Administration of Marsilid gave excellent results. She is pictured two years later completely well. The level of Marsilid in spinal fluid has been found to be 50 per cent higher than in other body fluids.



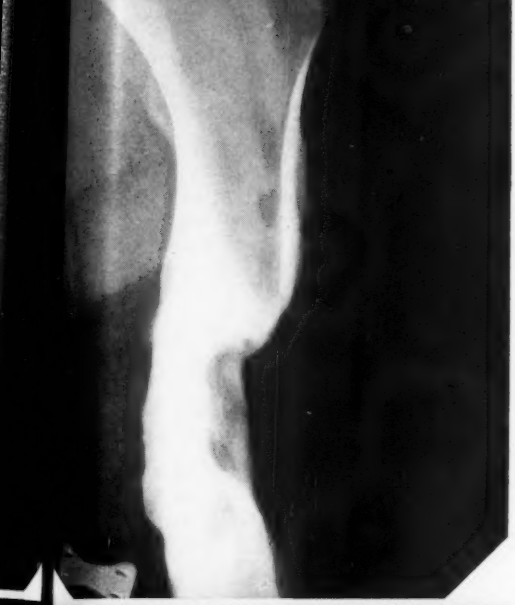


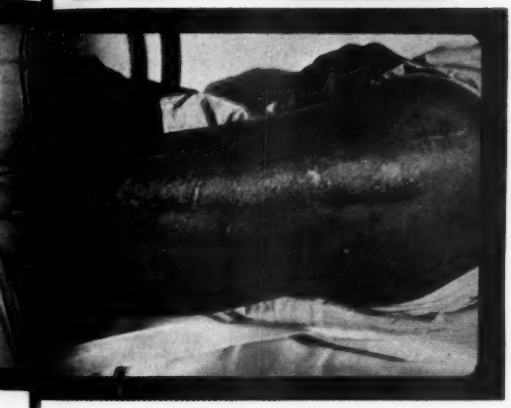




Interesting use has been made of Marsilid in the treatment of resistant wound healing.

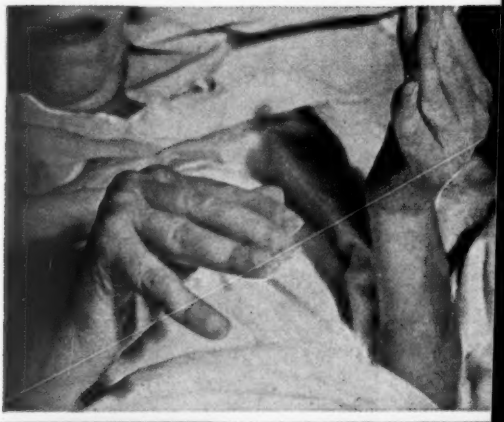
A compound fracture was suffered by this patient. Over a four year period, the wound would not heal, in spite of adequate antibiotic therapy. Repeated roentgenograms of the thigh failed to reveal any reason for the lack of healing. Finally, after administration of Marsilid, sufficient decalcification took place to demonstrate a sequestrum, which was removed. The wound then healed per premium.





Personality improvement and clearing of arthritic complaints has been achieved with Marsilid therapy.

Because of severe rheumatoid arthritis, this patient had been using a hot water bottle for relief of pain. This resulted in a severe burn, which finally healed when the patient was placed on Marsilid therapy. Surprisingly the arthritic symptoms also cleared to a great degree after a few weeks of Marsilid therapy.

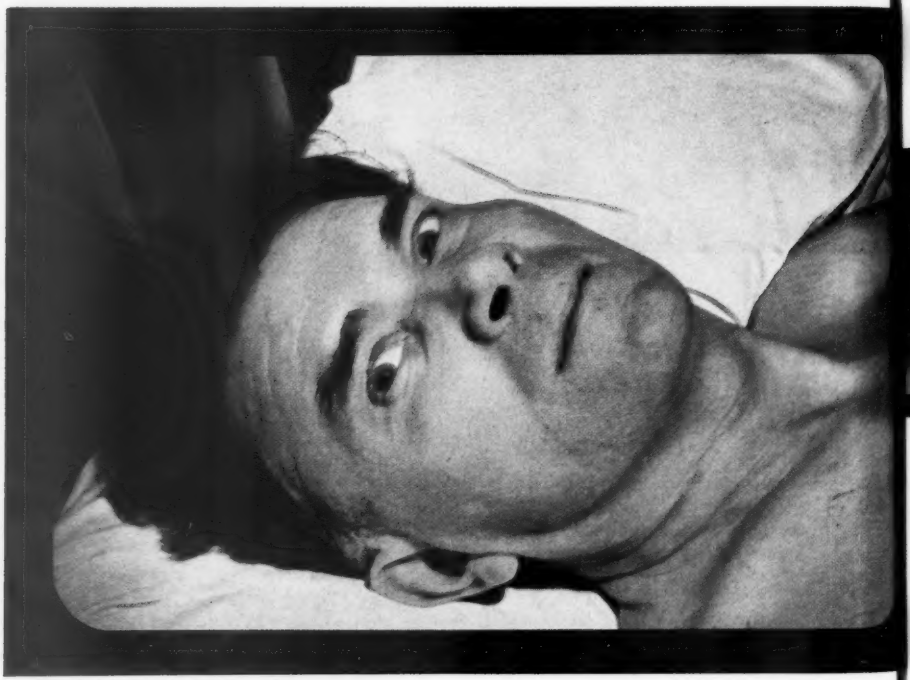


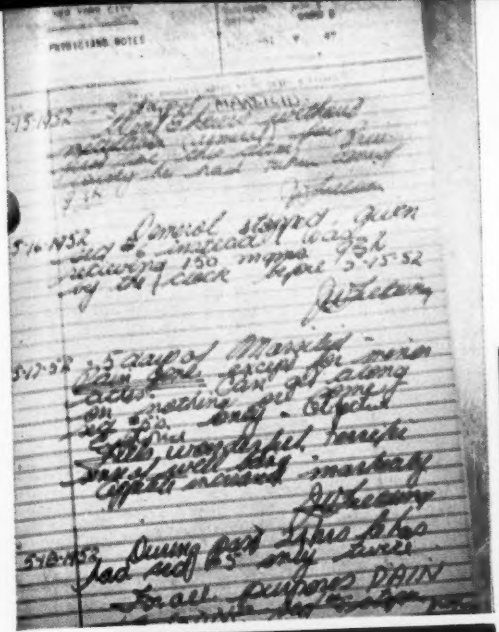
The patient having undergone a total gastrectomy overcomes weight loss and severe depression with Marsilid.

Top left: This patient, who had undergone a total gastrectomy, was unable to eat well and had suffered severe weight loss. Administration of Marsilid was begun (2 mg./Kg.) and the patient gained 20 pounds in one month. This weight gain has been maintained by continued administration of ½ mg./Kg. of Marsilid daily.

The dispirited patient with hypernephroma, who is addicted to narcotics, shows an excellent response to Marsilid.

The presence of hypernephroma in this patient had been proved. Because of severe pain, increasing doses of narcotics were required. The patient suffered weight loss and depression; he was unable to move his thigh because of the intense pain. After administration of Marsilid, no narcotics were required and the patient was free of pain; he was able to move his thigh freely. There were no withdrawal symptoms. A weight gain of 60 pounds occurred, and the patient was comfortable and in good spirits until the time of death.



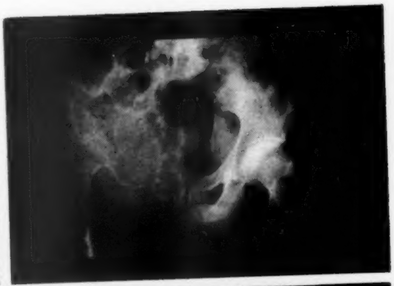

NEW YORK CITY
PHYSICIANS NOTES

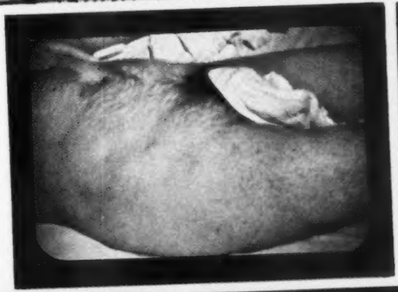
5-15-1952 [illegible]

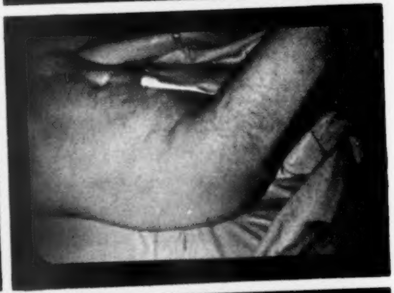
5-16-1952 Demerol stopped [illegible] receiving 150 mgms [illegible] before 5-15-52

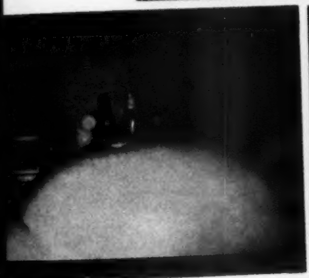
5-17-52 5 days of Marsilid [illegible] pain gone except for minor aches. Can get along on nothing [illegible] feels wonderful [illegible] appetite increased markedly

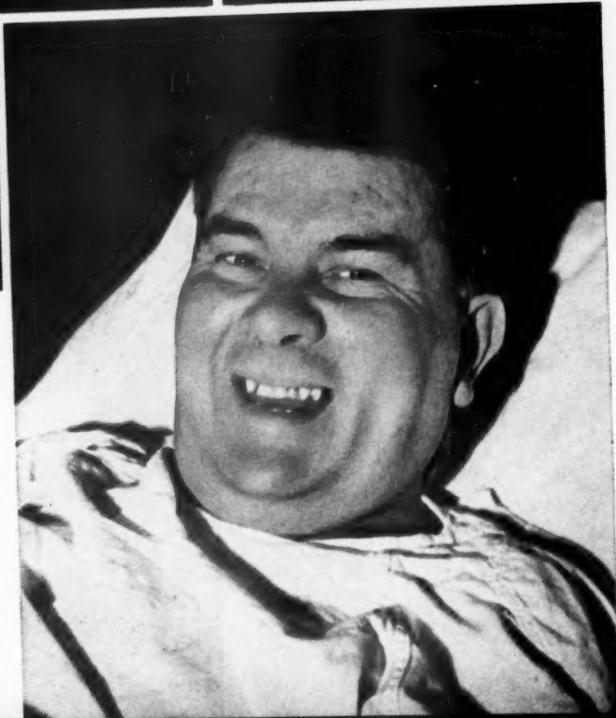
5-18-1952 During past [illegible] has had [illegible] only twice. For all purposes PAIN [illegible]

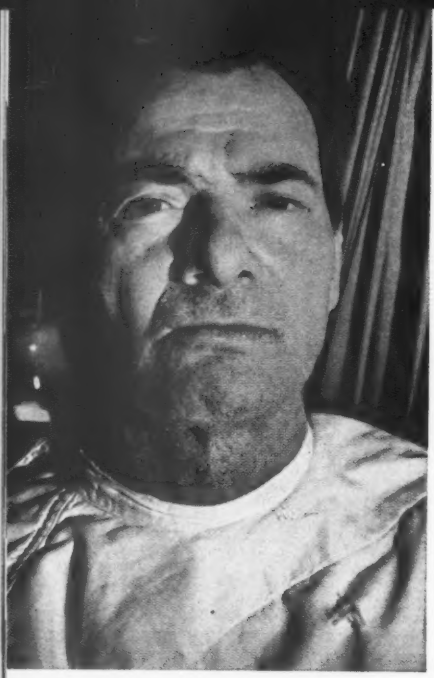


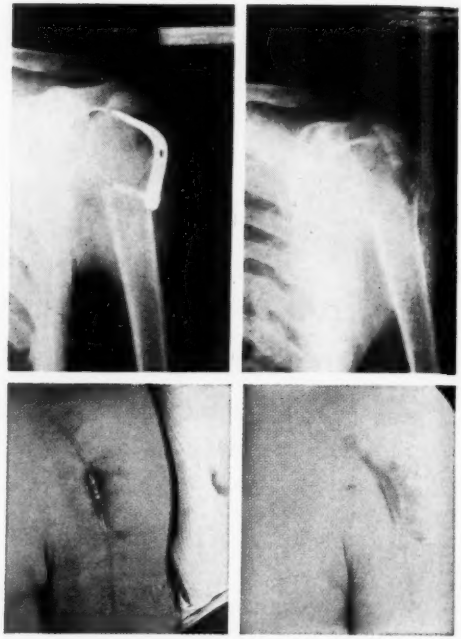






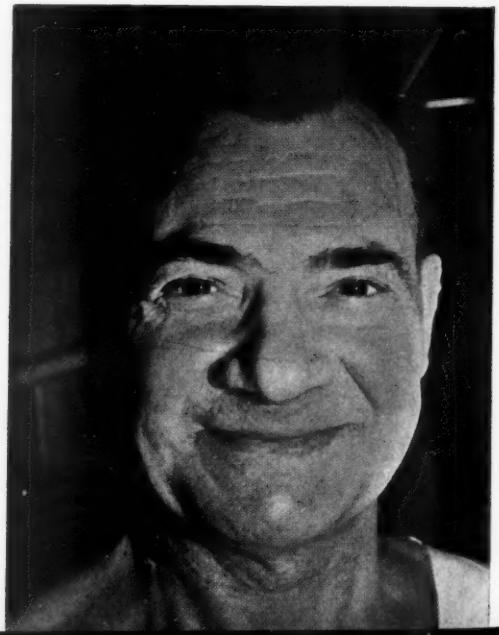






A marked change occurs in a dejected patient with a longstanding nonresponsive lesion secondary to compound fracture.

This patient had suffered a compound fracture. The fracture was treated with a plate, but the wound did not heal, although adequate antibiotic therapy had been employed. Administration of Marsilid for four weeks resulted in complete healing. Note the euphoria.



Enzymologic Effects of Marsilid and Related Hydrazine Derivatives

*Ernest Albert Zeller, M.D., Ph.D.**

CHICAGO, ILLINOIS

It has been shown that Marsilid† is a powerful inhibitor of monoamine oxidase of the brain and other organs. The question arose, therefore, as to whether or not monoamine oxidase is involved in the action of this drug on the central nervous system.

A great deal of biochemical, enzymologic, pharmacologic, and clinical investigation has already been done. It is impossible in this short time to review all that has been observed in this and in other laboratories, and the discussion will be limited to a few points, particularly to structural relationships and to some *in vivo* experiments.

Figure 1 shows the structure of Marsilid. It is interesting to note that the isopropyl residue may act as a hydrophobic force and that the hydrazine group, endowed with a rigid structure and strong dipole may behave as a nucleophilic agent. According to Kaplan and his co-workers Marsilid can be incorporated into a diphosphopyridine dinucleotide analogue, indicating that the isonicotinyl residue of Marsilid displays some remarkable chemical activity, too.

We must remember that many acyl hydrazides and hydrazine derivatives belong to the group of carbonyl reagents. Although Marsilid does not belong strictly to this class of compounds, it may mimic some of the properties of these reagents.

A series of enzyme-free model reactions were carried out by letting N,N′-dimethylhydrazine interact with acetic aldehyde. In figure 2, line A represents the ultraviolet absorption curve of 17 millimolar acetic aldehyde, B of 17 millimolar dimethylhydrazine, C of 8.4 millimolar acetic aldehyde plus 8.4 millimolar dimethylhydrazine, and D of 17 millimolar acetic aldehyde plus 17 millimolar dimethylhydrazine. Evidently, curves C and D do not arise by simple superposition of the optical densities of the individual components. Thus we conclude that this hydrazine derivative, in spite of the N,N′-di-substitution, is able to react with aldehydes, presumably by sharing a pair of electrons with these compounds. However, this type of mechanism is excluded as an explanation for the interaction between monoamine oxidase and Marsilid, because acyl hydrazides, the classical carbonyl reagents, are without influence on this enzyme.

Figure 3 shows the inhibitory power of Marsilid as a function of time. The top curve represents the oxygen uptake in the system of liver mitochondria and tyramine. Marsilid is added at 3, 6, and 12 minutes before the substrate is tipped in. The degree of inhibition increases with time. In a recent article, Davison confirmed and amplified this observation. This result could be interpreted by the assumption that Marsilid is converted into a more effective inhibitor before it reacts with monoamine oxidase.

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* Professor of Biochemistry, Northwestern University Medical School, Chicago, Illinois.

† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

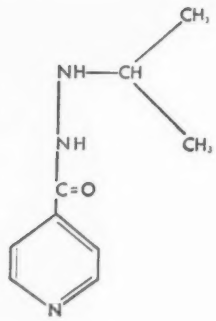

FIG. 1. Structural formula of Marsilid (iproniazid).

In table I a representative selection is given of far more than a hundred hydrazine derivatives tested. Hydrazine itself is practically without effect, its pI being 2 or less than 2. The negative logarithm of the concentration, which produces 50 per cent inhibition, is listed as pI. The introduction of one methyl group into the hydrazine molecule enormously increases the inhibitory power; methyl hydrazine happens to be one of the best inhibitors of monoamine oxidase. With a second methyl group the effectiveness drops, although N, N-dimethylhydrazine remains a fair inhibitor. However, when the second methyl group is introduced into the other nitrogen, as in N,N′-dimethylhydrazine, almost all activity is lost. When the second substituent is an acyl group, such as the isonicotinyl residue, the activity

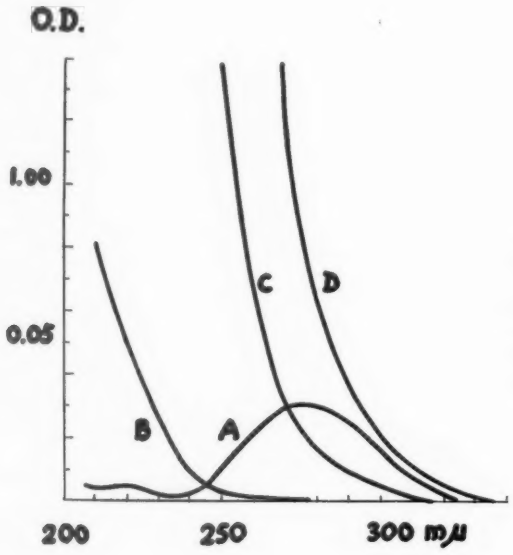

FIG. 2. Optical densities of mixtures of acetic aldehyde and N,N′-dimethylhydrazine. Curve A, 16.7 mM acetic aldehyde; curve B, 16.7 mM; curve C, mixture, both components at 8.35 mM; and curve D, mixture, both components at 16.7 mM.

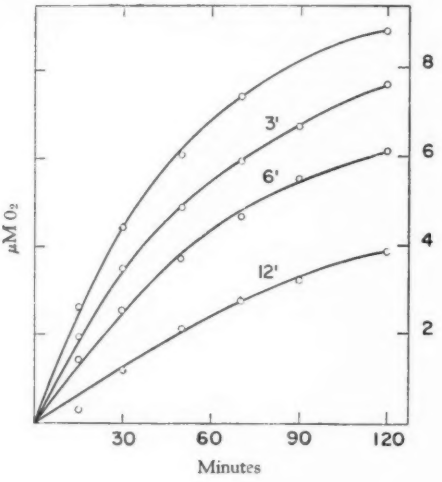

FIG. 3. Effect of time of incubation on the action of Marsilid on monoamine oxidase.

is only slightly reduced. These observations are of importance for the analysis of the reactive site of this enzyme.

We also compared the inhibitory power of a homologous series of aliphatic hydrazines and, similarly, we determined the rate of degradation of a homologous series of aliphatic amines as substrates of monoamine oxidase. The optimal aliphatic chain of the hydrazines was 1 to 2 units shorter than the aliphatic residue of the amines. Obviously, with respect to spatial arrangements, the NH group of the hydrazines is equivalent to a CH_2 group of the amines. This result again is in accord with the concept that substrates and hydrazines attach themselves to the same part of the surface of monoamine oxidase (table II).

We then tried to find the common denominator in the structure of numerous compounds, which turned out to be either suitable substrates or effective inhibitors of our enzyme. Both classes seem to react with the same spot on the reactive site of monoamine oxidase and, therefore, both must fulfill similar structural requirements. Both, either as amines or pseudoamines, form a covalent bond with the enzyme, breaking up a particular bond of the amine oxidase. After dehydrogenation and deamination of the substrate, the reaction products are released and the enzymic bond is reestablished. In the case of hydrazine derivatives,

TABLE I

Effect of Various Hydrazine Derivatives on Monoamine Oxidase

Derivatives	pI-50 Values
Hydrazine	2
Methylhydrazine	5.8
N,N-dimethylhydrazine	4
N,N′-dimethylhydrazine	2.7
N-isonicotinyl-N′-methylh.	4.5

TABLE II

Effect of Substrate Concentration on Inhibition of Monoamine Oxidase by Marsilid

Concentration of Tyramine (M)	NH_3 Produced without Inhibitor (10^{-6} mole)	Inhibition	
		1×10^{-4}M Marsilid Added Simultaneously (%)	1×10^{-5}M Marsilid Preincubated (%)
0.05	3.6	1	84
0.01	4.3	47	88
0.002	3.5	69	80

the hydrazine residue remains firmly attached to the enzyme, resulting in an irreversible inhibition.

According to Dr. Davison, the enormous inhibitory strength of Marsilid depends on its dehydrogenation by monoamine oxidase; the dehydrogenated product is attached to the enzyme. This concept seems to be supported by the general inhibitor pattern of monoamine oxidase. However, the dehydrogenated products are much less effective than the corresponding hydrogenated compounds. In addition, Marsilid contains an alpha-methyl group, which should prove to be an insurmountable obstacle in the dehydrogenation of amines and hydrazines.

Space does not permit discussion of the influence of Marsilid on other enzymes, in spite of the fact that in many laboratories some interesting studies have been carried out with this substance. No enzyme, with the possible exception of diamine oxidase, has a pI that comes close to the pI values found for monoamine oxidase. It is surprising that, so far, no amino acid oxidase is found to be affected by hydrazine derivatives, not even by compounds that may be considered pseudoamino acids.*

The question of the sensitivity of diamine oxidase must be brought in at this point. When this enzyme is prepared from various sources, considerable differences are found from one species to another. Diamine oxidase of rabbit liver displays a similar sensitivity toward Marsilid as monoamine oxidase, whereas human and porcine diamine oxidase appear to be more resistant. In any event, one has to keep in mind that Marsilid may block diamine oxidase *in vivo*. Actually, the metabolism of histamine and other diamines can be thoroughly changed by Marsilid, as demonstrated by Schayer with isotopically-labelled compounds.

Figure 4 proves that monoamine oxidase is not only inhibited *in vitro*, but also *in vivo*. The experiments, which were carried out in 1952, demonstrate that, after the administration of 10 mg./Kg. of Marsilid, the monoamine oxidase activity of rat liver homogenate, rat liver mitochondria, and brain mitochondria drops sharply, as compared with the untreated controls. Isoniazid is, as expected, without influence.

Thanks to the cooperation of two other laboratories in our medical school, it was possible to demonstrate the potentiating effect of Marsilid on certain sympatheticomimetic amines. In figure 5 the slight contraction of the cat nictitating membrane after administration of tyramine is recorded. In the same animal and with the same dose of tyramine a tremendous

* Prepared by Professor H. Erlenmeyer in Basel, Switzerland.

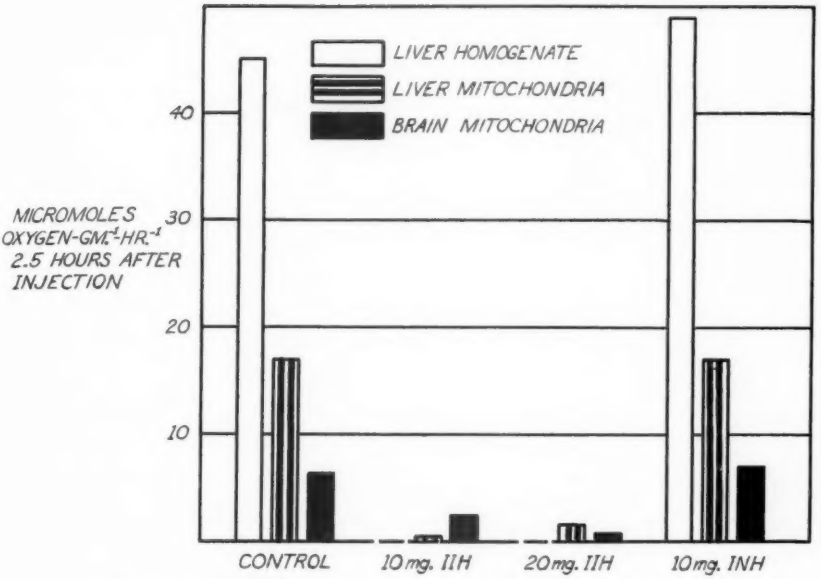

FIG. 4. *In vivo* inhibition of liver and brain monoamine oxidase by Marsilid.

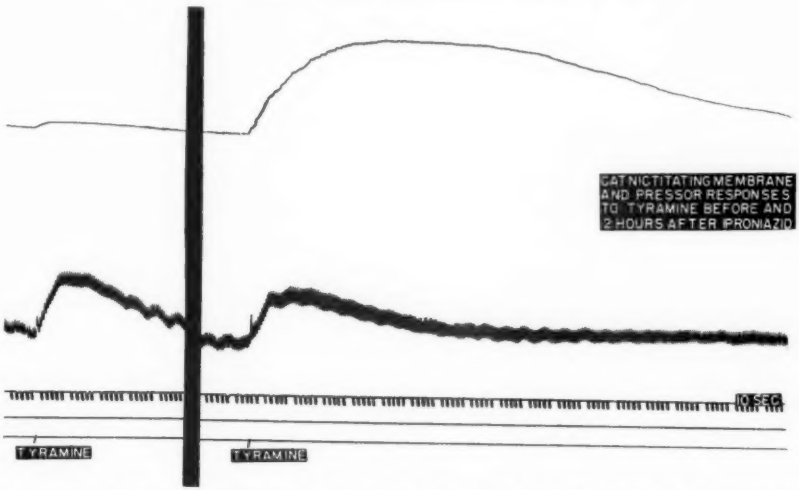

FIG. 5. Effect of tyramine and Marsilid on the nictitating membrane of the cat. From top to bottom, nictitating membrane, carotid blood pressure, time in 10 second intervals, and zero blood pressure. Left, 5.7 by 10^{-3} mM tyramine intravenous; right, repeat dose of tyramine two hours after 0.18 mM/Kg. of Marsilid.

contraction was produced two hours after the cat had received Marsilid. It may also be mentioned here that in many ways the chemical structural formulas of epinephrine and Marsilid are closely related. It was, therefore, not so surprising to find that both compounds seemed to compete for the same receptor or receptors of the rabbit aorta.*

Since these early studies, many outstanding investigators have used with great ingenuity this tool of the *in vivo* inhibition of monoamine oxidase by Marsilid. They unearthed and accumulated a great number of important facts about the metabolism and biological role of biogenic amines such as serotonin and the catechol amines.

In conclusion it should be again pointed out that in the body and brain unknown entities may exist that are the primary targets of Marsilid. Much work remains to be done before we can put more trust in our present concepts regarding the mode of action of Marsilid. However, at the present, from a great deal of physiologic, pharmacologic, and biochemical information, it can be interpreted uniformly that monoamine oxidase is one of the primary points of attack of Marsilid.

RESUME

Une étude relative à l'inhibition de la monoamine-oxydase a été entreprise pour tenter d'expliquer les effets du Marsilid sur le système nerveux central. La discussion de ces travaux a été limitée à des commentaires sur les rapports structuraux, les études *in vivo* et la monoamine-oxydase en tant qu'objectif du Marsilid. La conclusion de l'étude est qu'en dépit de l'existence dans le cerveau et d'autres parties du corps d'agents indéterminés, qui sont l'objectif du Marsilid, de nombreuses études métaboliques et pharmacologiques ont démontré que l'effet du Marsilid peut être compris si l'on admet que l'activité du Marsilid est dirigée sur la monoamine-oxydase.

Discussion

DR. HERBERT WEISSBACH:† We have noted from Dr. Zeller's presentation that Marsilid is a potent inhibitor of monoamine oxidase. The importance of this enzyme is obvious. This monoamine oxidase very likely plays an important role in the inactivation of such compounds as serotonin, the catecholamines, and their methoxy derivatives.

I would like to discuss briefly two aspects of our work that are essentially an extension of Dr. Zeller's original work on Marsilid and monoamine oxidase. The first deals with a soluble monoamine oxidase preparation that we have studied, and the second with the effect of Marsilid on the *in vivo* metabolism of amines.

Monoamine oxidase, as Dr. Zeller has shown, is found primarily in the mitochondria of the cell. However, in our preliminary experiments, on trying to purify this enzyme, we did not get a purified preparation that we could study. We looked, therefore, for a monoamine oxidase present in the supernatant fraction of the cell, and we did a tissue distribution study.

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* Experientia. 11:182, 1955.

† Laboratory of Clinical Biochemistry, National Heart Institute, Bethesda, Maryland.

In getting this enzyme, we centrifugalized the homogenate and then tested the supernatant fraction for activity. We did not expect a potent monoamino oxidase in the supernatant fraction, since we knew that most of the activity was in the mitochondria. However, in guinea pig liver, there is an active enzyme in the supernatant fraction that we have been able to study more thoroughly. This enzyme has only one-tenth the activity of the mitochondrial enzyme. It can be purified and concentrated.

We have purified the enzyme twenty to thirtyfold and have been able to study the over-all reaction of monoamine oxidase on serotonin. *In vivo*, the reaction proceeds through an intermediate, which has never been isolated, but what we can see is the end product, 5-hydroxyindole acetic acid. Using the purified preparation, we have been able to separate the two steps, the first step being the oxidation of the amine to the aldehyde and the second step the oxidation of the aldehyde to the acid.

The second step (the aldehyde to the acid) has been shown to require aldehyde dehydrogenation. In the over-all reaction of the amine to the acid, if a suitable substrate is incubated such as serotonin, a monoamine oxidase, and an excess of aldehyde dehydrogenase and DPN added, complete conversion of the end product to 5-hydroxyindole acetic acid can be obtained.

In the course of this conversion, the diphosphopyridine nucleotide becomes reduced, and the reaction can be conveniently measured by determining the rate of diphosphopyridine nucleotide reduction. Using this enzyme, it is possible to eliminate the second step, the aldehyde reaction, leaving out the aldehyde and the hydrogenase or diphosphopyridine nucleotide, and then stopping the reaction at the aldehyde stage. In doing this, we have been able to accumulate the aldehyde produced from serotonin as well as the catecholamines, and we hope in the near future to obtain sufficient quantities of these compounds to test their physiologic activity.

On the second aspect of our work, concerning the effect of Marsilid on amine metabolism *in vivo*, Dr. Zeller has shown that if tissues are removed from animals after Marsilid treatment, complete inhibition of monoamine oxidase is obtained, and this lasts for several days.

Along this line, we thought that if Marsilid was administered to animals, a striking effect should be shown on the serotonin levels, especially in tissues in which there is a rapid turnover of serotonin, such as in brain tissue. In rabbits and rats given a large dose of Marsilid, a rapid increase occurs in the brain serotonin levels, and the levels double in several hours.

We then extended this work on administration of Marsilid and serotonin to animals. We had thought that if Marsilid was administered to animals and the rate of disappearance of the amine measured in the intact animal (mice were used since we had been assaying the whole animal) a significant effect on serotonin disappearance in the Marsilid-treated animals would be shown. However, when we measured the rate of disappearance of serotonin in animals pre-treated with Marsilid at a dose completely inhibitory of monoamine oxidase, we found essentially the same rate of disappearance as was found in the normally untreated control subjects.

This can be explained in two ways. One is that Marsilid was not blocking all the monoamine oxidase *in vivo* and that there was enough of the enzyme left to metabolize the amines,

and the other is that there are other pathways of serotonin metabolism which, when monoamine oxidase is blocked, can take over and metabolize the compound.

As a test to see if monoamine oxidase was active in these Marsilid-treated animals, we looked for 5-hydroxyindole acetic acid. In the Marsilid-treated animals, when serotonin was being destroyed at essentially the same rate as in normal animals, practically no 5-hydroxyindole acetic acid was formed. In untreated animals, when serotonin was being destroyed, 35 per cent of the serotonin destroyed could be accounted for by 5-hydroxyindole acetic acid.

We looked, therefore, for other routes of metabolism and, starting with radioactive serotonin, we showed that in a normal animal 30 per cent of the serotonin goes to 5-hydroxyindole acetic acid, and that 20 per cent of the serotonin metabolized goes to another product that could not be identified. In the Marsilid-treated animal, however, no 5-hydroxyindole acetic acid was formed. Instead, this other metabolite, which accounted for 20 per cent of the serotonin and which was destroyed in the normal animal, now accounted for as much as 90 per cent of the serotonin metabolized.

We have now been able to obtain some information as to the structure of this metabolite. Although we have several milligrams of it, we do not have it in pure form. It is not a 5-hydroxyindole acetic acid. It is, however, an indole, and very likely it is a conjugate of the serotonin on the 5 position, that is, the hydroxy group. The compound has a free amine group, since it is a weak substrate of amine oxidase.

It is important to consider the possibility that, in Marsilid-treated animals or patients, normal metabolic pathways, such as metabolism of amines to monoamine oxidase, may be blocked, that side pathways may take over, and that the accumulation of these products, which normally are found in small amounts, may play a role in the mechanism of the action of Marsilid.

CHAIRMAN SIDNEY UDENFRIEND:* I would like to continue discussion of Dr. Zeller's paper.

DR. KOELLE: Dr. Zeller, what would be the Pi-50 value for Marsilid of the hydrazines on the table you showed?

DR. ZELLER: Five.

DR. FOX: Can you tell us something about the hydrophobic effect of the isopropyl? You did not elaborate, but I assume you are aware, which is surprising to those of us in our laboratory, that Marsilid is more soluble than isoniazid, despite the presence of the isopropyl group, which should decrease its water solubility. It happens to be much more water soluble than isoniazid.

DR. ZELLER: I thought that the isopropyl group would help to get Marsilid into the cell in the brain, because isopropyl has such a high affinity for lipids. But the point where these hydrophobic effects certainly have played a role is in the combination with the enzyme. I have shown that the length of the chain is of greatest importance for the reaction between the enzyme and the inhibitor of the enzyme and substrate, and that at least one methyl group is needed, as an ethyl group is needed, for an amine to be bound to the surface of the enzyme. The only interpretation is that this side chain acts as a hydrophobic group and combines with other hydrophobic groups on the surface of the enzyme.

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CHAIRMAN UDENFRIEND: When you speak of solubility, do you mean absolute solubility? I think distribution between water and organic solvents might be important. Have you any information on that?

DR. FOX: Actually what you say is true. In the distribution effect, Marsilid is simultaneously more soluble in water and more soluble in organic solvents.

CHAIRMAN UDENFRIEND: That, I think, would be a determining thing.

DR. BOSWORTH: Don't both of these papers tend to show that the action of Marsilid is not cumulative, although the by-products may increase during the administration, that they tend to fade out at a normal rate as soon as Marsilid is stopped, and that there is no real cumulative effect? I would like to hear the opinion on that.

CHAIRMAN UDENFRIEND: I think, Dr. Zeller, you could say something about the long-lasting effects of Marsilid on the enzyme level.

DR. ZELLER: The effect is long-lasting. In experiments with rats, it lasted approximately five days. This action, this recovery after five days, is still open to question as to whether it is a recovery of enzyme or a reformation of enzyme. I think that it is the latter, but we have no direct evidence.

DR. LANGEMANN: I am wondering about the cell sites to which Marsilid goes. Has Marsilid been shown to enter the cell, going to some parts in the cell (the mitochondria, for instance)? What amounts do you find at such cellular sites? How long does it stay? If it goes to the mitochondria alone, does it stay in the mitochondria?

DR. ZELLER: I do not have any information on that. I have asked many workers in the field, because this question of how much Marsilid enters the cell is of paramount importance. There is, in brain, an enzyme that is blocked *in vivo*, but Marsilid is not present in liver.

Obviously, there are two explanations: that Marsilid does not enter the liver cell at all, or that it is destroyed at the same rate at which it enters. Therefore, detailed studies on the entrance and persistence of this drug within the cell are needed. I know of no such studies.

CHAIRMAN UDENFRIEND: The only thing that we could get from that, Dr. Langemann, is that even the soluble enzyme is blocked in the same way for as long a period. Isn't that true?

One other possibility, Dr. Zeller, is that in other tissues the pathway might play a more important role than in the brain, so that even if monoamine oxidase is blocked uniformly in all tissues one tissue might have another enzyme that the other does not.

DR. BESSMAN: Just one question. Is the effect of Marsilid on the soluble monoamine oxidase the same as its effect on the particulate form?

DR. WEISSBACH: We have not done a complete study except *in vivo*, and in this case soluble monoamine oxidase has the same effect.

DR. ZELLER: I want to confirm Dr. Weissbach's statement. We have done quite a few studies on soluble enzyme preparations, which we solubilized from mitochondria, and, although there are some minor differences, the soluble enzyme reacts in essentially the same way as the particulate. That applies even for the time reaction. We thought at first that it would take time for Marsilid to enter the mitochondria and to hit monoamine oxidase, but the time curve is the same for soluble enzyme, so it is not a matter of penetration or permeability, but it is a matter of the enzyme itself.

DR. SCHERBEL: Dr. Zeller, is there any relationship between amine oxidase in the brain, the liver, and in the peripheral tissues, as far as their metabolic alterations are concerned? In other words, if one is up, can the other be down; or does the monoamine oxidase activity in the liver have no relationship to that in the peripheral tissues?

DR. ZELLER: I cannot say anything on that. It is hard to answer.

CHAIRMAN UDENFRIEND: Since the answer was so short, we will take Dr. Bessman's last question.

DR. BESSMAN: I would like to ask Dr. Zeller if he has any information regarding the activity of monoamine oxidase in the heart. Did you do any experiments on inhibition of monoamine oxidase in the heart?

DR. ZELLER: Dr. Langemann, who is here, was the first one to determine the presence of monoamine oxidase in the heart. In our studies, we have tested practically every tissue, but I must admit that I do not recall exactly how it is regarding the heart. I would say offhand that it is inhibited and that we have worked on it, or I would have remembered it.

DR. LANGEMANN: We have investigated monoamine oxidase in heart mitochondria, and it behaves in much the same way as the monoamino oxidase from liver mitochondria. But I did not investigate the effect of Marsilid on these preparations. I found a curious behavior, a different behavior, in mitochondria from liver. I could get a fair amount of nitrogen from these mitochondria, but only one third of the activity from liver mitochondria. From a very few experiments with heart mitochondria, I think it would attack tryptamine at a higher rate than tyramine.

CHAIRMAN UDENFRIEND: We have had an interesting discussion. I am sure that many of the points still undiscussed will be brought up in the final open discussion.

Pharmacologic Significance of Inhibition of Monoamine Oxidase

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Selective inhibitors of specific enzymes have proved extremely useful tools in biochemistry and physiology. Examples include the cyanide, malonate, and fluoroacetate ions as inhibitors of cytochrome oxidase, succinic dehydrogenase, and aconitase, respectively. Several therapeutic agents, including acetazolamide, the mercurial diuretics, and the antibiotics and chemotherapeutic agents probably act chiefly by enzyme inhibition. The anticholinesterase agents are outstanding examples of both physiologic tools and clinically useful drugs. The scope of pharmacology lies between, or may overlap, physiology and therapeutics. One of its primary aims is the determination of the biochemical or physiologic mechanisms by which drugs produce their therapeutic effects. The pharmacologic problem to be considered here may be stated briefly. Iproniazid (Marsilid†) is an inhibitor of monoamine oxidase. When given to patients and laboratory animals, it produces certain effects. Are these pharmacologic effects of Marsilid due to inhibition of monoamine oxidase and the consequent accumulation of the enzyme's endogenous substrates, or are they dependent upon other actions of the drug?

Monoamine oxidase was discovered in 1928 by Dr. Mary Hare Bernhein,[1] who used the term tyramine oxidase to describe the enzyme responsible for this activity of liver homogenates. The literature on the properties, distribution, inhibitors, and possible physiologic functions of monoamine oxidase was reviewed thoroughly and critically by Blaschko[2] in 1952. Hence only certain points from earlier studies that are particularly germane to the present discussion need be noted here.

In 1937, Blaschko, Richter, and Schlossmann[3] demonstrated that monoamine oxidase can oxidize epinephrine; Blaschko[4] showed also that ephedrine competitively inhibits the oxidation. Shortly thereafter Gaddum and Kwiatkowski[5] published an interesting account on the interactions of ephedrine with epinephrine, or sympathetic nerve stimulation, on the perfused rabbit's ear. The addition of ephedrine to the perfusion fluid was found to potentiate the vasoconstrictor response to epinephrine or to the stimulation of the sympathetic trunk; colorimetric assay of the effluent indicated that more of the infused epinephrine was recovered in the presence than in the absence of ephedrine. From these results, the authors proposed that ephedrine might act primarily by inhibiting monoamine oxidase, resulting in the accumulation of epinephrine (or, in terms of our present knowledge, norepinephrine) liberated from sympathetic nerves. Thus its action with respect to the adrenergic nervous system was presented as analogous to that generally assumed for physostigmine in the

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

cholinergic system. It has frequently been overlooked in references to this article that Gaddum and Kwiatkowski also mentioned several alternative mechanisms that could explain their findings. In a report by Richter and Tingey,[6] which appeared the following year, it was shown that ephedrine is so weak an inhibitor of monoamine oxidase that, in the concentrations employed by Gaddum and Kwiatkowski, inhibition of the enzyme was probably negligible. Furthermore, cobefrine (the α-methyl analogue of norepinephrine) is not oxidized by monoamine oxidase, but its actions also are potentiated by ephedrine.[7] Another objection to the proposed mechanism of action of ephedrine is the low velocity of oxidation of epinephrine and norepinephrine by monoamine oxidase *in vitro*. Moreover, in contrast to the relatively high concentrations of acetylcholinesterase present in cholinergic neurons of the cat,[8] histochemical studies have revealed no preferential distribution of monoamine oxidase in adrenergic neurons or adrenergically-innervated effector organs in this species. In the rabbit, however, monoamine oxidase appears to be more concentrated in adrenergic than in other types of neurons.[9] There are several enzymes in mammals in addition to monoamine oxidase that are also capable of destroying epinephrine and norepinephrine, including cytochrome oxidase,[10] DOPA-oxidase (tyrosine oxidase),[11] and conjugases.[12] Their possible participation in the metabolism of epinephrine and norepinephrine has been discussed in several review articles.[2, 13–19] Most recently it has been found that O-methylation probably constitutes another pathway for the metabolism of epinephrine.[20]

One of the most important factors in the elucidation of the role of acetylcholinesterase in cholinergic transmission has been the availability of potent, relatively specific inhibitors, particularly those of the irreversibly reacting alkylphosphate type. The discovery by Zeller and his associates[21] that iproniazid exerts such an effect on monoamine oxidase *in vitro*, whereas its close analogue isonicotinic acid hydrazide (isoniazid) does not, appeared to provide a similar agent, which did not have the limitations of low potency and rapid reversibility characteristic of ephedrine.

The first extensive studies of the pharmacology of iproniazid revealed no particular effects suggestive of preservation of endogenous epinephrine or norepinephrine.[22, 23] Furthermore, the injection of doses sufficient to produce apparently nearly complete inactivation of monoamine oxidase in cats failed to potentiate the effects of intravenously injected epinephrine on the blood pressure or nictitating membrane,[24, 25] although the action of tyramine was intensified.[24] Nevertheless, studies of the effects of iproniazid on the fate of isotopically labeled epinephrine in mice indicated that the compound diverted to other metabolic pathways a considerable fraction that would otherwise have been oxidized by monoamine oxidase.[26]

In our own laboratory, in collaboration with K. Kamijo and H. H. Wagner, the effects of high equimolar doses of iproniazid and isoniazid were compared on the response of the cat's nictitating membrane to stimulation of the cervical sympathetic trunk and intra-arterial injection of epinephrine, norepinephrine, and tyramine.[27] Results were somewhat complex, but after repeated experiments a fairly consistent pattern emerged. Following either iproniazid or isoniazid, the response of the nictitating membrane to adrenergic nerve stimulation or injection of the amines was first reduced; iproniazid caused a more consistent and

greater initial reduction in contraction than did isoniazid. After thirty to sixty minutes, the height of contraction then usually rose significantly above the control level. The increased response was, on the average, greater after isoniazid than after iproniazid, excepting with tyramine; iproniazid caused a marked prolongation of the tyramine response.

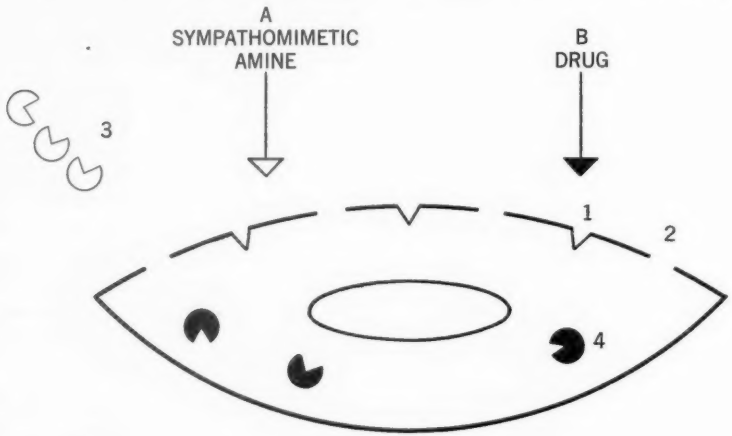
In attempting to interpret these findings, it was suspected that the initial reduction in contraction after iproniazid or isoniazid might be due to adrenergic blockade. Assays with the isolated rat's seminal vesicle showed that both drugs possess this action, and that iproniazid is a considerably stronger adrenergic blocking agent than isoniazid. A report to the same effect was published at that time by Zeller and his associates.[28]

The increased responsiveness of the membrane, which followed the temporary decrease, was more difficult to explain. Manometric assay of homogenates of the brain, liver, and kidney removed after each experiment indicated that iproniazid had produced practically complete inactivation of the monoamine oxidase in all three organs, whereas there was no significant difference between the values for the animals who had received isoniazid and the control subjects. Therefore, monoamine oxidase inhibition could account only for the markedly increased response to tyramine. Measurements *in vitro* indicated that neither oxidation by the cytochrome oxidase system, nor auto-oxidation of epinephrine or norepinephrine, was affected significantly by moderate concentrations of iproniazid or isoniazid. It appeared, therefore, that the potentiating effect of the hydrazide was probably due to an action other than enzyme inhibition. A similar conclusion was reached ten years earlier by Dawes,[29] who found that a series of amidines and guanidines potentiated the cardiovascular action of intraportally injected epinephrine; some of the active compounds were inhibitors of monoamine oxidase, whereas others were not. Dawes therefore proposed that the potentiation might be due to interference with the uptake of epinephrine by the hepatic cells. Blaschko[18] has suggested a similar mechanism to account for the potentiating effect of ephedrine on the action of sympathomimetic amines, and has pointed out that prevention of access of the amines to the enzyme *in vivo* would simulate inhibition of the enzyme. Another possible explanation of the potentiation is suggested by a recent report of Bovet and his associates[30] on the potentiating effect of B-diethylaminoethyldiphenylpropylacetate hydrochloride (Smith, Kline & French Laboratories 525-A) on several neuromuscular blocking agents. The mechanism of potentiation here is apparently not interference with the metabolism of the agents, but displacement of the latter by the potentiator from plasma protein and other nonspecific receptors, to which both are adsorbed.

On the basis of these findings, the possible pharmacologic interactions of norepinephrine with iproniazid and other drugs might be summarized as shown in figure 1. Following its injection or its liberation from an adrenergic axon, a molecule of norepinephrine (A) might combine with a receptor site (1) of an effector cell and produce its characteristic effect. If it passes through the membrane (2) of the same or another cell, or is adsorbed to plasma protein (3), it is removed from the field of activity. Following its eventual combination with monoamine oxidase or another enzyme (4), it is metabolized. A second drug, such as iproniazid, by virtue of its structural similarity to norepinephrine can react at all or some of these sites. At the receptor site it may produce a sympathomimetic effect or, as in the

case of iproniazid, adrenergic blockade. By combining at sites 2 or 3, it can delay the rate of disappearance of norepinephrine from the field of activity and thus potentiate its effect. Inhibition of the enzyme (4) will also cause potentiation if the enzymatic destruction of norepinephrine is a limiting factor in the degree or duration of its action; otherwise it will bring about only a quantitative alteration in its metabolism. In contrast to iproniazid, isoniazid, is less effective at site 1, and at moderate doses ineffective at site 4; it may be equally effective at sites 2 or 3. It should be emphasized that the latter sites have been included more or less by default, since their roles as diagramed are not based on any direct evidence. It is, of course, quite possible that an unconsidered mechanism is responsible for both termination of the action of norepinephrine and the potentiating effect of the hydrazides.

Let us now consider the possible interrelationships between the actions of iproniazid and 5-hydroxytryptamine. The latter compound was first identified in platelets by Rapport[31] in Page's laboratory, where the designation serotonin was introduced. Erspamer and



SITE	EFFECT	
	A.	B.
1. Receptor	Sympathomimetic	Sympathomimetic or Adrenergic Blockade
2. Pore (same or adjacent cell)	Termination of Action	Potentiation of A-1
3. Plasma Protein	"	"
4. Enzyme (MAO)	" or Gradual Destruction	" or Modified Metabolism of A

FIG. 1. Possible sites of mutual action of a sympathomimetic amine (for example, norepinephrine) and a second drug (for example, iproniazid) at an autonomic effector cell. See text for discussion.

Asero[32] then showed that enteramine, a principle that Erspamer had found in several marine organisms and in the mammalian gastrointestinal tract, is also 5-hydroxytryptamine. The distribution and action of 5-hydroxytryptamine have been reviewed fully by both Page[33] and Erspamer.[34] The oxidation of 5-hydroxytryptamine by monoamine oxidase[35] probably represents the chief if not the sole initial step in its metabolism;[36] a considerable proportion of administered or endogenous 5-hydroxytryptamine is excreted in the urine as 5-hydroxyindole-acetic acid.[37]

5-Hydroxytryptamine is formed in the brain and elsewhere by the decarboxylation of 5-hydroxytryptophane.[38] The concentrations of 5-hydroxytryptamine and the decarboxylase show wide variations in the different regions of the brain. Although there is some suggestion that they parallel each other, there are outstanding exceptions.[39] Cerebral monoamine oxidase is most concentrated in the hypothalamus, but the variations in its concentrations throughout the brain are not striking.[40]

Udenfriend, Weissbach, and Bogdanski[41] have found that 5-hydroxytryptamine is unable to cross the blood-brain barrier readily, but administered 5-hydroxytryptophane does and is then decarboxylated to 5-hydroxytryptamine in the brain. When groups of animals were given iproniazid, it caused an increase in the cerebral levels of both endogenous 5-hydroxytryptamine and the concentration of 5-hydroxytryptamine reached following the injection of 5-hydroxytryptophane.[42] At first consideration, this seemed attributable to the inhibition of monoamine oxidase, for when the brain and peripheral organs were removed and homogenized, their monoamine oxidase activities were found to be almost completely suppressed. However, additional findings placed this interpretation in doubt. Iproniazid had no significant effect on the level of 5-hydroxytryptamine in the total carcass following administration of 5-hydroxytryptophane. Furthermore, when the monoamine oxidase activities of the brains and livers of iproniazid treated animals were determined by the tissue-slice, in contrast to the homogenate technique, the degrees of inhibition of the enzyme were found to be slight. The authors therefore suggested that iproniazid probably does not gain access *in vivo* to monoamine oxidase, but does so only after subsequent removal and homogenization of tissues. Since the enzyme is present chiefly in the mitochondria and microsomes,[43] this explanation seems reasonable. What then, is the explanation for the increased levels of 5-hydroxytryptamine in the brain following administration of iproniazid, and the potentiation by iproniazid of the pharmacologic actions of iproniazid plus either 5-hydroxytryptophane[44] or the 5-hydroxytryptamine-releasing agent, reserpine?[45]

Although inhibition of monoamine oxidase may contribute to these effects, factors such as those discussed previously with respect to the potentiation of norepinephrine and epinephrine by iproniazid and isoniazid are possibly of greater importance. Additional actions of iproniazid, such as its reactions with pyridine nucleotides[46] and its effect on pyridoxine levels,[47] may also be the basis of some of its pharmacologic effects. The pharmacologic adage that no drug has a single action should never be overlooked. Thus the choline phenyl ethers, which are moderately potent inhibitors of monoamine oxidase,[48] have in addition a wide spectrum of stimulating and inhibitory actions at various sites in the central and peripheral nervous systems.[49]

A clue to the importance of enzyme inhibition in bringing about the actions of a drug may be obtained by conducting parallel studies with chemically closely related compounds that are not potent inhibitors, as was done in the previously quoted investigations of the actions of amidines and guanidines,[29] and iproniazid and isoniazid.[27] Whenever possible, this type of control should be employed.

Recent histochemical studies with bisquaternary anticholinesterase agents, which penetrate cell membranes poorly, have indicated that their cholinomimetic effects may result from the inhibition of only the externally oriented acetylcholinesterase, which probably represents a small fraction of the cell's total enzyme.[50] It is possible that a similar situation exists with respect to monoamine oxidase, that is, that a small amount of the cell's monoamine oxidase exists at the surface, and that this portion is primarily responsible for the relatively rapid oxidation of amines. Unfortunately, the histochemical methods available at present for determination of monoamine oxidase are not sufficiently sensitive or accurate to test this possibility. However, by focusing future investigations at the cellular level, more specific information may be obtained concerning the significance of enzyme inhibition as a mechanism of drug action.

RESUME

Dans les expérimentations comparatives effectuées par l'auteur sur les effets du Marsilid par rapport à ceux de l'isoniazide sur l'injection intra-artérielle d'adrénaline, de noradrénaline et de tyramine, chez le chat, on a observé que, la tyramine exceptée, la réponse était plus marquée avec l'isoniazide. La détermination manométrique d'homogénats de cerveau, de foie et de rein, réséqués après l'expérimentation, a révélé que le Marsilid avait entraîné l'inactivation presque complète de la monoamine-oxydase dans les trois organes, tandis qu'aucune différence n'existait entre les valeurs enregistrées chez les animaux recevant l'isoniazide et chez les animaux-témoins. Ce n'est donc que l'inhibition de la monoamine-oxydase qui pouvait expliquer l'accroissement de la réponse à la tyramine.

En se fondant sur ces données, les interactions possibles entre la noradrénaline et le Marsilid sont les suivantes: à la suite de son injection ou de sa libération à partir d'un axon adrénergique, une molécule de noradrénaline peut se combiner au niveau de la terminaison réceptrice d'un effecteur et produire son effet caractéristique. Si elle traverse la membrane de cette cellule ou d'une autre cellule, ou si elle est adsorbée sur une protéine plasmatique, elle est éliminée du champ d'activité. A la suite de sa combinaison ultérieure avec la monoamine-oxydase ou avec un autre enzyme, elle est métabolisée. Le Marsilid, en raison de sa similarité structurale avec la noradrénaline, peut réagir à tous ces points ou à certains d'entre eux. Au niveau de la terminaison réceptrice, la noradrénaline peut produire un effet sympathomimétique ou, en ce qui concerne le Marsilid, un blocage adrénergique. Lorsque celui-ci se combine en d'autres points, il peut retarder la disparition de la noradrénaline du champ d'action, d'où potentialisation de son effet.

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Discussion

Dr. Amedeo Marrazzi:* Obviously it is not possible to discuss adequately all the points that Dr. Koelle has taken up. Nevertheless, I would like to emphasize that in these days,

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TABLE I

Iproniazid Inhibition of Monoamine Oxidase Activity of Rat Brain and Liver Fractions

	Brain			Liver		
	μM NH_3/Gm./hour			μM NH_3/Gm./hour		
Preparation	Control	Iproniazid (10^{-2} M)	Inhibition (%)	Control	Iproniazid (10^{-2} M)	Inhibition (%)
Homogenate	9.5 (6)*	6.8 (6)	27	27.1 (6)	27.7 (6)	−2.7†
Debris	2.7 (7)	1.9 (7)	26	14.1 (7)	10.4 (7)	28
Mitochondria	8.1 (4)	4.6 (4)	43	19.7 (4)	11.9 (4)	43

* Numbers in parentheses represent the number of experiments made in each case.

† The difference between the percentage of inhibition of brain and liver homogenates gives a P value <0.01 using the t test.

when we all use the receptor concept in our daily thinking, it is useful indeed to have the more sophisticated and illuminating discussion that Dr. Koelle has given us.

Perhaps it is also useful to express it in another way. It seems that a paraphrase of a simple algebraic term is applicable here, namely, that things related to the same thing are related to each other. I think Dr. Koelle's diagram illustrates it beautifully. If you add to that the varying affinities of substances in question for reactor sites, whether they are on the cell membrane, in the cell, or in the surrounding medium, and the fact that the final action is determined by the amount of substance present, that is, by the tonus of the tissue involved, the supply of the substance, you then have a considerable series of permutations and combinations for which to account. It is rather remarkable that things do follow some rule of thumb predictions.

TABLE II

*Inhibition of Monoamine Oxidase Activity of Rat Brain Cell Fractions by Iproniazid**

	Debris			Mitochondria		
	μM NH_3/Gm./hour			μM NH_3/Gm./hour		
Control		Iproniazid ($2x10^{-2}$ M)	Inhibition (%)	Control	Iproniazid ($2x10^{-2}$ M)	Inhibition (%)
2.4 (4)†		1.4 (4)	43	7.1 (4)	3.4 (4)	52

* Mince incubated for one hour with iproniazid, then washed, homogenized and centrifugalized.

† Numbers in parentheses represent the number of experiments made in each case.

TABLE III

Iproniazid Inhibition of Monoamine Oxidase Activity of Rat Brain and Liver Minces

Experimental Group*	Brain			Liver		
	μM NH_3/Gm./hour			μM NH_3/Gm./hour		
	Control	Iproniazid ($2x10^{-2}$ M)	Inhibition (%)	Control	Iproniazid ($2x10^{-2}$ M)	Inhibition (%)
1	5.1 (4)†	3.8 (4)	26	10.1 (4)	9.4 (4)	−3.5‡
2	4.2 (3)	2.6 (3)	44	12.4 (3)	4.9 (3)	60

* In group 1 the activity of the minces was determined without washing; in group 2 the minces were incubated with iproniazid for one hour, washed, and the activity of the minces determined.

† Numbers in parentheses represent the number of experiments in each case.

‡ The difference between the percentage of inhibition of brain and liver minces gives a P value <0.05 using the t test.

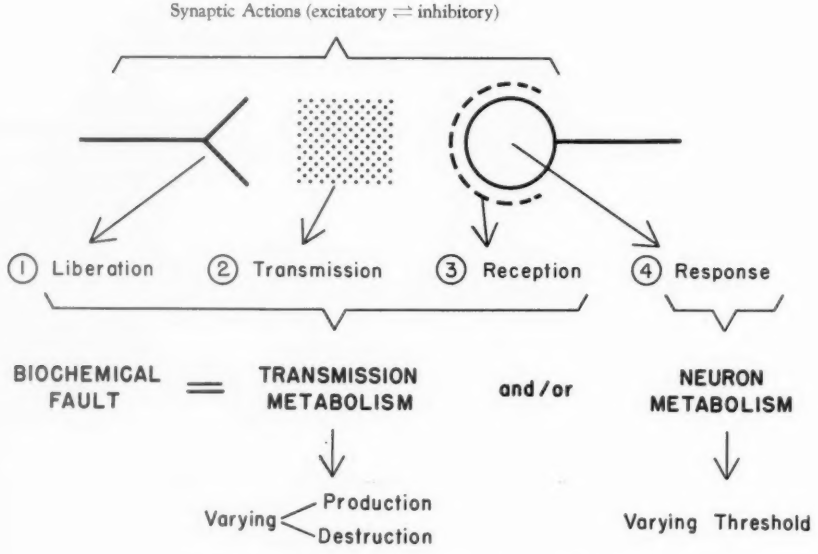

FIG. 1. Potential factors in disturbed synaptic equilibrium.

On some of the points that Dr. Koelle brought up, we have some specific data that I would like to show you. Table I shows the action of Marsilid on various fractions. Notice the brain particularly. The percentage of inhibition, as you see, is high in the mitochondria; and in the debris, which may also contain the strategically located monoamine oxidase on the cell surface, the total amount is small, of course, and the percentage of inhibition does not appear to be large when it is compared to the other fraction.

However, when iproniazid is added to the whole cells in the form of minces, the large percentage difference in inhibition between the debris, presumably cell membrane monoamine oxidase, and the rich mitochondria monoamine oxidase, is gone (table II). So perhaps there really is something to think about regarding the idea of strategically located enzymes at the site where many of these substances are believed to really act on the cell membrane.

The difference between activity in the brain and in the liver has created a great deal of interest (table III). Work on this was done in collaboration with Dr. Gluckman of our laboratories. Dr. Gluckman believed that the difference was due possibly to a water soluble substance circulating in the blood. Compare the usual preparation of the mince to which the iproniazid has been added to the same preparation, which has been washed. By introducing the possibility of washing out a water soluble inhibitor, we find that the difference has lessened between the inhibition in the brain and in the liver.

I would like to go to another point which needs introduction (fig. 1). We have been inter-

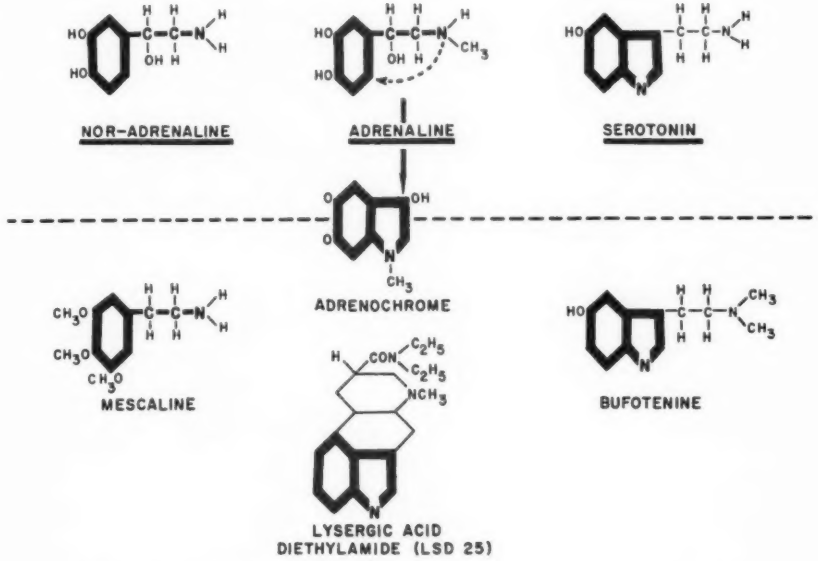

FIG. 2. Relation of cerebral inhibitory neurohumors to exogenous psychotogens.

ested in the same sort of a picture, particularly with respect to the possibilities of biochemical fault at the synapse, either in transmission of impulse or in the response of the cell itself. Of course, this involves production and destruction. Therefore, the enzymatic problem is involved.

The particular interest in iproniazid stems from the fact that the sympathomimetic amines and indoles such as serotonin (fig. 2) are endogenous substances and will produce synaptic inhibition, which we have recorded at various sites of the nervous system, particularly the cortex. Some related substances can be regarded as chemical psychotogens. They are chemically related and produce the same kind of synaptic inhibition.

Figure 3 shows a central preparation in which we stimulate on one side and record from the terminal synapse on the other. The injection is put into the common carotid artery. Thus we expose the ipsilateral cortex to the drug before anything else so that the other cortex, the other hemisphere, can be used as a control. By dilution in the general blood stream, the concentration becomes subthreshold for peripheral effects. The situation we are trying to influence is the equilibrium, recorded symbolically in the lower right corner, between cholinergically excitatory substances and adrenergically inhibitory substances, including serotonin.

Serotonin seems to be particularly important because it is plentiful in the brain and because, if ranked in order of activity, including all the exogenous and endogenous compounds, serotonin and dimethyl serotonin are very high indeed (fig. 4).

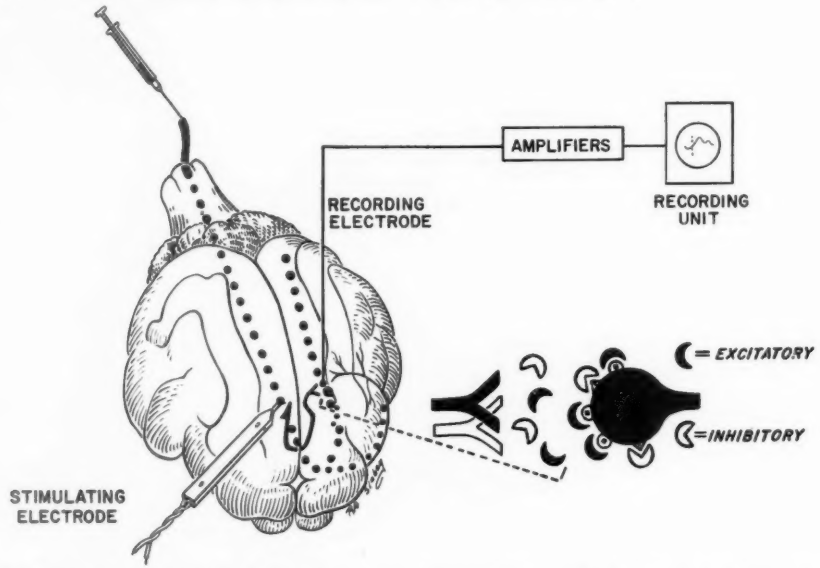

FIG. 3. Transparent model of the brain; two neuron intercortical (transcallosal) pathways; schematic blood supply (arterial) pathway for injected material.

Figure 5 is a record of the evoked response, as well as the electrocorticogram showing control, maximum inhibition, and recovery.

We wanted to assure ourselves of some correlation between data bearing not only on injected serotonin, which produced the effect, but on *in situ* serotonin as well. The only way this can be done is by preserving it with iproniazid. We then wanted to know whether

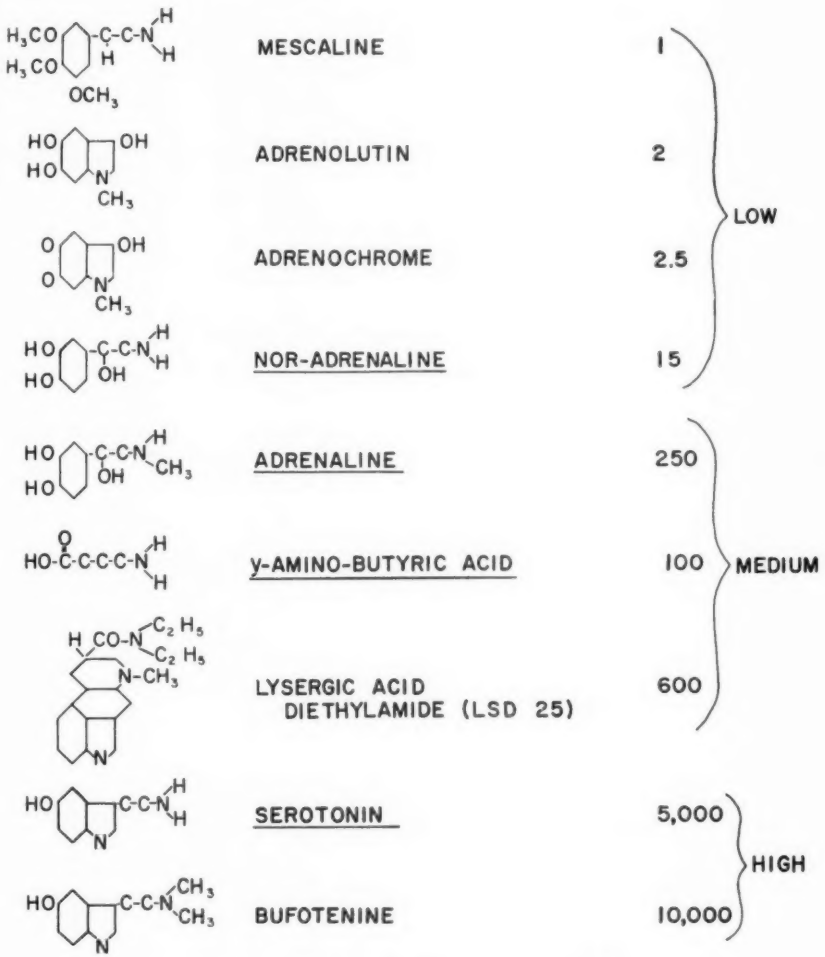

FIG. 4. Cerebral synaptic inhibitory potency in the cat.

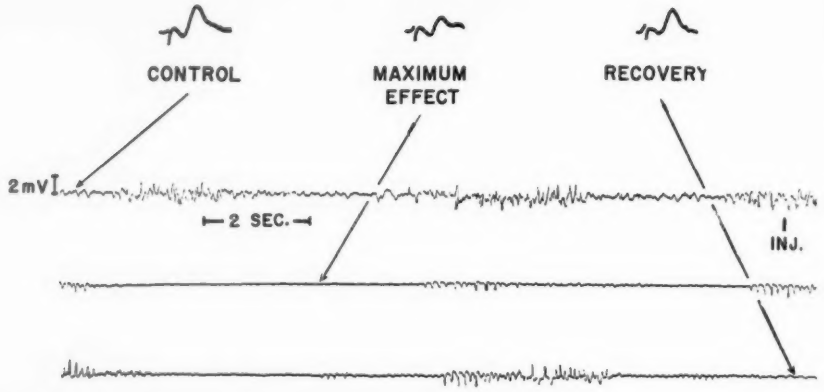

FIG. 5. Action of iproniazid on simultaneously recorded evoked potentials and electrocorticogram; common active electrode on ipsilateral suprasylvian gyrus; iproniazid (10 mg./Kg.) administered into the common carotid artery.

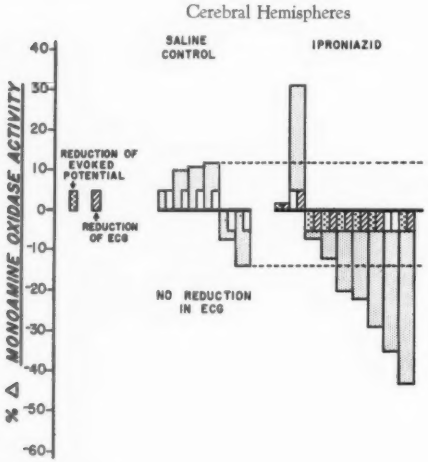

FIG. 6. Correspondence of differential iproniazid inhibition of monoamine oxidase and electrical activity in the brain; iproniazid (10 mg./Kg.) administered into the common carotid artery (cat, sodium pentobarbital).

or not, there was a difference in monoamine oxidase activity or titer between the two halves of the brain at the time of maximum inhibition (fig. 5). The control subjects are indicated on the left side (fig. 6). There is a small variation between the two halves of the brain. After administration of iproniazid, at the time of maximum inhibition, there is a considerable reduction on the injected side as compared to the other or control side.

We think, then, that iproniazid does effect cerebral function and dysfunction in terms of upsetting the balance of humoral control of synaptic inhibition.

Psychic Action of Isoniazid in the Treatment of Depressive States

J. Delay and J.-F. Buisson†*

PARIS, FRANCE

During 1952, we collaborated at the Clinic for Mental Diseases on an investigation concerning the possible psychical action of isoniazid. We believe it may be useful to recall the results in connection with the discussions dealing with the psychical action of a closely related substance, iproniazid.‡

When, in the course of treatment with isoniazid, favorable modifications were observed in the psychic state of tuberculous patients, the majority of phthisiologists attributed them to the improvement of the pulmonary condition. Consequently, several authors, who were using isoniazid for tuberculous patients with mental disease, interpreted the improvement from the standpoint of the antituberculous action of isoniazid as applied to "mental forms of tuberculosis," or to "psychoses of tuberculous origin."

We tried, on the contrary, to demonstrate and to utilize the neuropsychical action of isoniazid, independent of its bacteriostatic efficacy. First, we shall recapitulate briefly the results of an objective psychological study made in the course of treatment with this drug on a group of patients with pulmonary tuberculosis.

For this study, we used the personality questionnaire of the Minnesota Multiphasic Personality Inventory. We know the results of this test can be expressed by a curve representing the psychologic profile. The different scales of which it is composed correspond to the different categories usually employed in psychiatric nomenclature. We applied this test to 13 patients treated for mental disorders. In 9 subjects, tuberculosis had been recently checked, and the lesions were moderate. We prescribed isoniazid in doses of from 250 to 300 mg./day for 6 patients, and of 500 mg. in the other 7 patients. In 8 patients, isoniazid was the only medication applied. The other 5 patients simultaneously received para-aminosalicylic acid. Each subject was examined twice, that is, before the initiation of treatment and after one month of treatment.

We shall not discuss the averages of the psychologic profiles of these patients as they were established before institution of treatment. They often differ notably from the usual normal profile, and the pathological predominances observed by us frequently indicated fairly marked schizoid tendencies. Comparison of these results with those obtained during the course of treatment demonstrated interesting modifications. In 9 patients, that is in 75 per cent of the observed subjects, the new psychologic profile (fig. 1) showed a definite amelioration, as expressed by a fall of the entire curve. Notice that this improvement was

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‡ Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

not accompanied by a rise in the hypomania scale, although the generally stimulating "psychotonic" action of the treatment might have led us to expect this. In fact, the improvement was subjectively felt by the majority of the patients under treatment as a sensation approaching euphoric dynamism; notably, it was felt in 2 patients in whom improvement of the psychical state was contrasted with the aggravation of the pulmonary condition. On the other hand, in 3 patients an interesting rise of the curves was noted, especially with respect to the scales designating hypomania, schizophrenia, and paranoia. In 2 of these patients, the profile showed only minor modifications without the appearance of any alarming clinical symptoms. In the third patient, the second profile showed an important aggravation involving the scales Sc, Pa, and Ma. In the course of the weeks following our examinations, we observed in this patient the development of mental disturbances characterized by subexcitation with persecution ideas in interpretative mechanism; however, we must admit that the pretherapeutic profile of this patient had already shown a frankly pathologic aspect, notably, an abnormal predominance in the scales of F, Pa, and Sc. With interruption of treatment, the disturbances subsided within a few weeks, and were parallel with abâtement of the subexcitation.

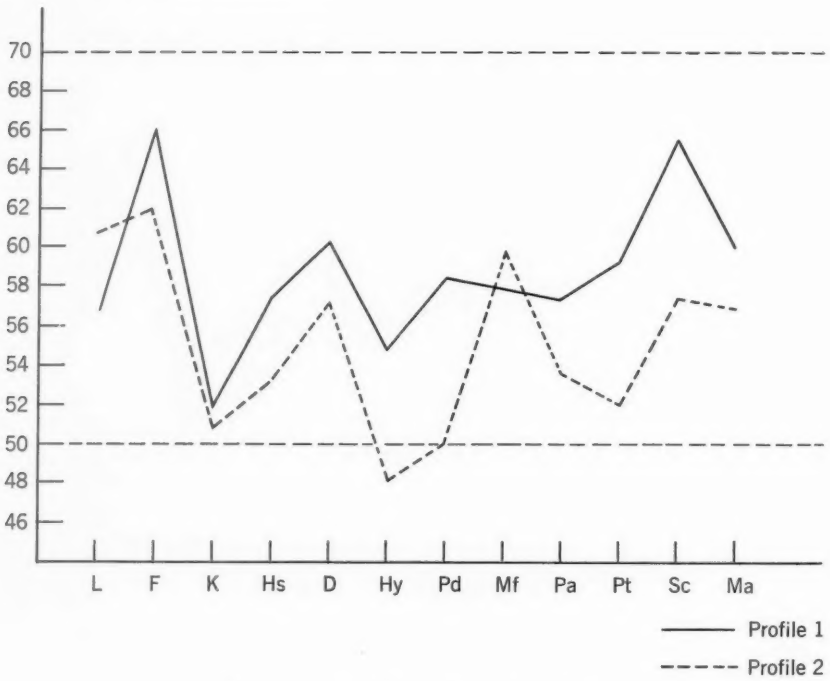

FIG. 1. Average profiles of a group of 9 subjects.

Beside this psychologic study, we also tried utilizing isoniazid in psychiatric therapy. Encouraged by its euphoriant influence, we administered isoniazid to mental patients who did not have tuberculosis. In December, 1952, we published our first results.[1] During the following months we tried this therapy on 20 patients, most of them suffering from severe psychic depression.[2]

METHODS AND RESULTS

We employed doses of 4 and 8 mg./Kg. administered orally and sometimes combined with intramuscular or intravenous injections. When massive doses of 10 mg./Kg. were given in a single daily injection for several days, either intravenously or intramuscularly, some good results were achieved. We think a true shock effect was thus accomplished, thereby enhancing the action of treatment with smaller doses. Improvement did not occur in all patients at the same period of treatment. In certain patients improvement was progressive after two or three weeks; in others it was perceptible from the third day. Sometimes we noticed the occurrence of intolerance symptoms, such as cramps, instability, psychomotor subexcitation, and insomnia. As a rule, these symptoms were easy to recognize when the evolution was carefully supervised. The disturbances always subsided rapidly after discontinuation of treatment or decrease of doses. For prophylaxis, we systematically added a daily dose of nicotinamide to the treatment. Finally, in 3 patients, the abrupt interruption of medication resulted in temporary incidents (insomnia, subexcitation, anxiety) and simulated an actual relapse into the depressive state. It seems that we were dealing here with true manifestations of weaning, which were also recognized by Selikoff and his collaborators.[3] By gradual termination of treatment, timed over a period of approximately a week, we seemed to avoid these phenomena.

In five typical patients with severe melancholia, improvement was manifest in consequence of this treatment, which permitted us to avoid recourse to seismotherapy (electroconvulsive therapy). Fearing a relapse, we prolonged treatment for two weeks after apparent recovery.

We observed undeniable improvement in 6 additional patients, rapid improvement in 3 patients from the first days on of treatment, and in the others improvement was noted toward the second week of treatment. However, this favorable result either could not be maintained in spite of continuation of treatment, or it was so inconclusive that recovery could not be attributed entirely to the medication. Finally, in 9 patients treatment had no effect or it resulted only in dissociated and insignificant improvement.

Subsequently, we utilized isoniazid for a greater number of less severe cases of depression, asthenic depressions, reactional depressions, or depressive episodes of asthenia or anxiety in the course of neurotic states. In these patients isoniazid gave us an interesting proportion of successful results in approximately 60 per cent of those treated.

The therapeutic action of isoniazid affects the appetite, weight, sleep, mood, and psychomotor activity. Frequently dissociated ameliorations were observed, especially during grave depressions, which affected more distinctly one or several of these properties. In some cases, we saw marked anxiety with active suicidal ideas succeeded by a peculiar

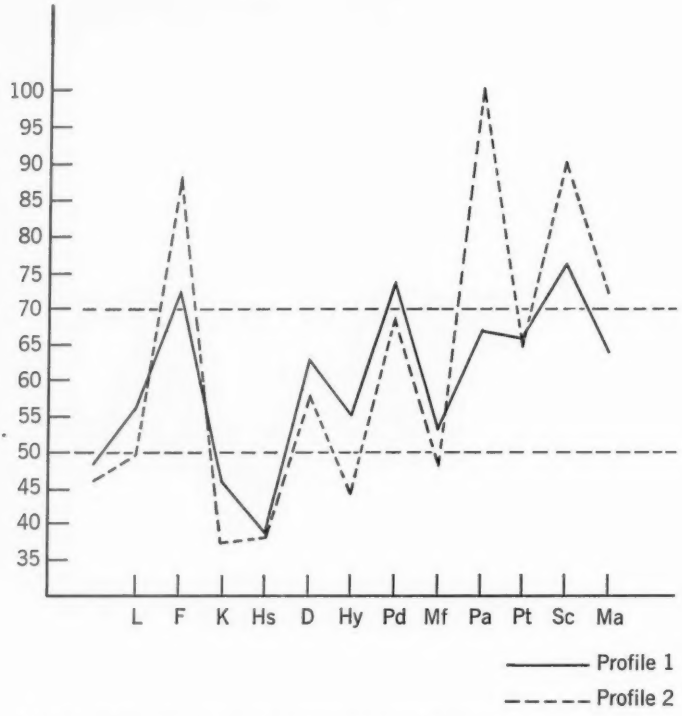

FIG. 2. Profiles of a subject who presented a psychotic episode during treatment.

picture in which indifference was associated with slowing of mental processes. Sometimes prolonged asthenia persisted after regression of anxiety. In contrast, the treatment provoked in other patients a state of subexcitation in which anxiety manifestations persisted or gradually became disseminated.

The return of appetite is often one of the first signs of the efficacy of the treatment. Sometimes we noted it as the only sign in the absence of any other improvement. Weight gain ran parallel with the return of appetite after several weeks of treatment in patients with depressive anorexia. However, the medication may possibly have a direct favorable effect on tissue anabolism. The stimulatory action of isoniazid on the appetite in nontuberculous subjects is still disputed. But we should remember that certain workers obtained good results in patients with mental anorexia.

SUMMARY

The action of isoniazid in persons with severe depressions is favorable, although very unstable and often dissociated. In persons with less severe depression states, isoniazid

seems to give good results in a fairly large number of cases. These cases justify analogous therapeutic trials with other synthetic substances chemically related to isoniazid.*

RESUME

L'action de l'isoniazide sur les individus fortement déprimés s'est montrée favorable, elle est toutefois instable et souvent dissociée. Dans les états de dépression moins sévère, de bons résultats sont obtenus avec l'isoniazide chez un assez grand nombre de malades. Ces résultats justifient la poursuite d'essais thérapeutiques analogues avec d'autres produits synthétiques apparentés chimiquement à l'isoniazide.

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* A comparative study of the actions of iproniazid and isoniazid is in progress at the Clinique des Maladies Mentales.

Possible Mechanism of Antidepressant Action of Marsilid

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It was found, not long after its discovery, that the major route of metabolism of serotonin is oxidative deamination by the enzyme monoamine oxidase.[1, 2] While it has been generally agreed that this enzyme is important in serotonin metabolism, its role in the metabolism of norepinephrine has remained an issue of controversy.

The suggestion has been made that both serotonin and norepinephrine act as neurohumoral agents in certain areas of the brain.[3] It would seem that if this were true, there should be a means of limiting quickly in the brain the physiologic action of norepinephrine as well as serotonin. On the basis of studies to be described, we have concluded that norepinephrine, as well as serotonin, is normally metabolized in the brain *in vivo* largely through the action of monoamine oxidase.[4]

Much of the experimental evidence that monoamine oxidase is not important in catecholamine metabolism is based on the use *in vitro* of tissue preparations. In brain homogenate, serotonin is a much better substrate of monoamine oxidase than is norepinephrine, being metabolized about five times more rapidly. The same ratio is obtained with monoamine oxidase preparations from liver, suggesting that the same enzyme is acting in both tissues. Moreover, enzymatic destruction of both amines can be completely blocked in brain and liver preparations by known monoamine oxidase inhibitors, such as Marsilid,† (10^{-3} to 10^{-4} *M*) or by cocaine or ephedrine (10^{-2} *M*). Thus it appears that in unfortified brain homogenates, only monoamine oxidase acts to destroy norepinephrine.

The metabolism of serotonin and norepinephrine was studied in the brain *in vivo* by utilizing the action of reserpine in liberating both amines from their storage depots. In these experiments,[4] reserpine was administered intravenously to rabbits and at various intervals the animals were sacrificed and the brain stems analyzed for norepinephrine and serotonin (fig. 1). It is noteworthy that the rates of disappearance of both substances are identical. At one hour, about 80 per cent of both of the amines had disappeared from the brain stem. However, when Marsilid was administered six hours before reserpine, the destruction of both amines was almost completely blocked, as indicated in table I.

The interesting parallelism between the rates of metabolism of brain serotonin and brain norepinephrine can be perhaps best explained by assuming that the rate limiting step in the metabolism *in vivo* of either substance is the rate of release rather than the enzyme-substrate affinity.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc., for iproniazid.

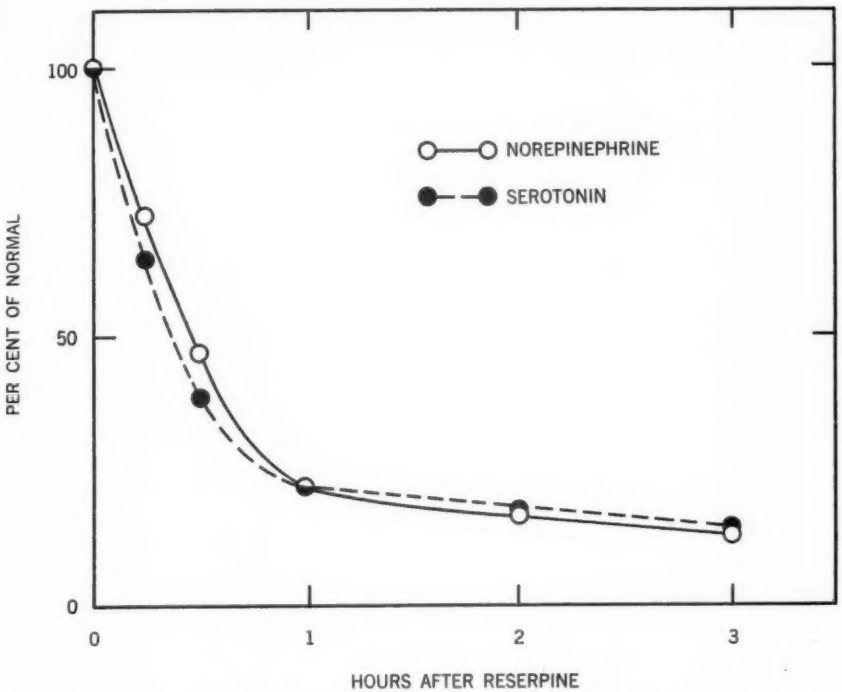

FIG. 1. Comparative rates of disappearance of norepinephrine and serotonin in rabbit brain stem after release by reserpine (5 mg./Kg.). Points at zero time represent the amine concentration in control animals. (From Shore et al.[4])

TABLE I

*Effect of Marsilid on Metabolism of Brain Serotonin and Norepinephrine after Release by Reserpine**

Injection	Average Serotonin Level (μg./Gm.)	Average Norepinephrine Level (μg./Gm.)
Marsilid	1.2	0.65
Marsilid plus reserpine	1.2	0.65
Reserpine	0.05	0.05

* Rabbits received Marsilid (100 mg./Kg.). After six hours some animals received reserpine (5 mg./Kg.). One hour later the animals were killed and their brain stems were analyzed. Another series of animals was given reserpine alone and the analyses were performed seven hours later. Figures represent the average of several values.

The identity of the norepinephrine released by reserpine in the presence of Marsilid was established by paper chromatography and fluorescence analysis. Thus, when monoamine oxidase was blocked *in vivo* no alternate major pathway of norepinephrine metabolism was disclosed, suggesting that in rabbit brain, methylation of norepinephrine hydroxyl groups or oxidation of the molecule to noradrenochrome represent at most only minor pathways.

In order to study a possible relationship of brain monoamine oxidase inhibition to the antidepressant pharmacologic effects of Marsilid that have been demonstrated in man, Marsilid was administered to rabbits and changes in brain serotonin and norepinephrine concentrations were measured.[5]

The administration of a single large dose of Marsilid (100 mg./Kg.) caused a marked rise in brain serotonin concentration and a lesser rise in norepinephrine (fig. 2). No obvious pharmacologic effects were evident following the single large dose of Marsilid.

However, when smaller doses of Marsilid (25 mg./Kg.) were administered daily, signs of sympathetic stimulation, including mydriasis, as well as a variable degree of excitation, appeared in three or four days, when the amine levels were about twice normal (fig. 3). Similar experiments in which the dose of Marsilid was 50 mg./Kg./day resulted in marked

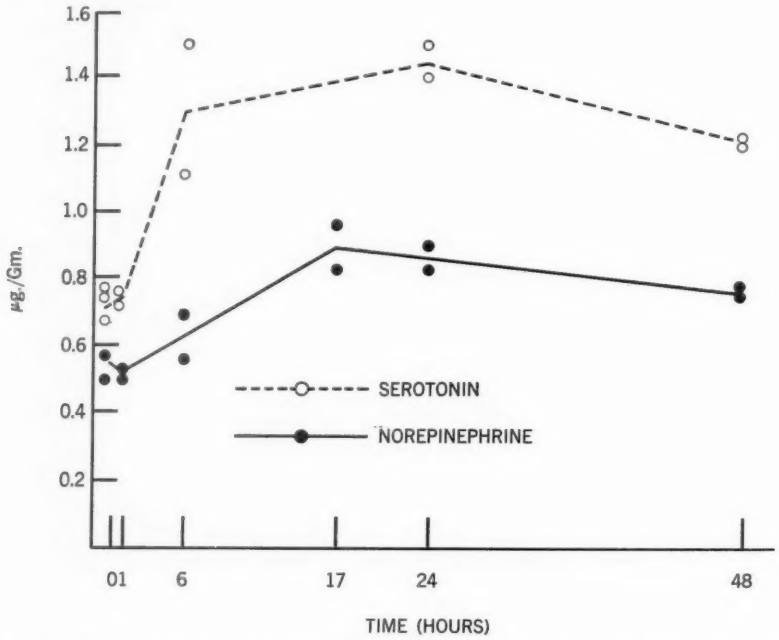

FIG. 2. Effect of a singe large dose of Marsilid (100 mg./Kg.) on serotonin and norepinephrine levels in rabbit brain stem. Each point represents the value from a single animal. (From Spector et al.[5])

excitement of the animals on about the third day, and serotonin and norepinephrine were again increased about two or threefold. With smaller doses of Marsilid (10 mg./Kg. daily) the onset of excitement and the two to threefold increase in brain amine concentration was noted only after four or five days.

Thus a temporal relationship can be demonstrated between the pharmacologic effects of Marsilid and an increase in the levels of brain serotonin and norepinephrine. It seems unlikely that the effects on the brain are produced by the drug *per se*, since the injection of a single large dose of Marsilid was without pharmacologic effect.

There are other indications that the central effects may have been produced by blockade of monoamine oxidase activity. Isoniazid, the free hydrazine congener of iproniazid, is a poor inhibitor of monoamine oxidase. Daily doses of 50 mg./Kg. failed to elicit either a rise in the concentration of the brain amines or central effects similar to those seen after administration of Marsilid, whereas another monoamine oxidase inhibitor, JB 516 (α-methyl, β-phenyl-ethylhydrazine, Lakeside Laboratories) after small daily doses increased brain serotonin and norepinephrine and caused central stimulation.

It is difficult to say whether the increase in serotonin or in norepinephrine is of the greater

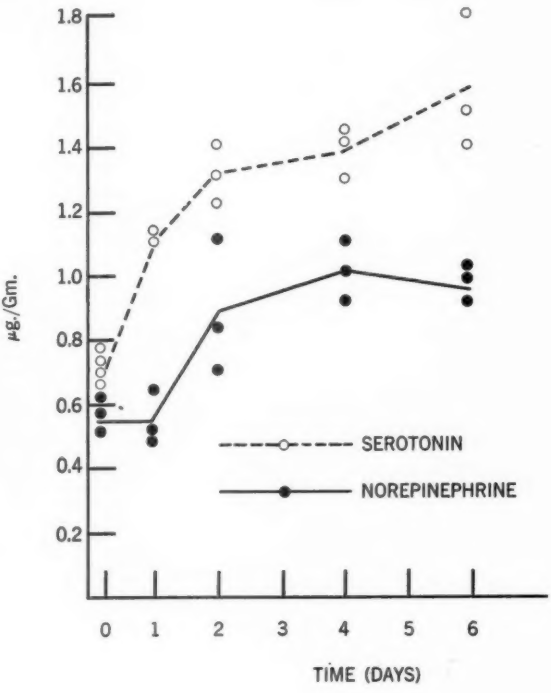

FIG. 3. Effect of daily doses of Marsilid (25 mg./Kg./day) on serotonin and norepinephrine concentration in rabbit brain stem. Each point represents the value from a single animal. (From Spector et al.[5])

importance in the central effects of Marsilid. Administration of the serotonin precursor, 5-hydroxytryptophan, has been shown to produce excitation[6] and similar effects have been observed after administration of the norepinephrine precursor, dihydroxyphenylalanine.[7] It does appear, however, that there is a correlation between the central stimulatory effects of Marsilid and its ability to block brain monoamine oxidase.

RESUME

Les données antérieures montrent que le métabolisme de la sérotonine consiste en une desamination par oxydation. La sérotonine et la noradrénaline exerçant dans le cerveau des fonctions analogues, l'auteur a supposé qu'une substance inhibant l'action de la sérotonine inhiberait également celle de la noradrénaline. En conséquence, la réserpine a été administrée par voie intraveineuse à des lapins qui ont été ensuite sacrifiés à différents intervalles. Quand la sérotonine et la noradrénaline ont été recherchées dans le tronc cérébral des animaux, on a découvert que la vitesse à laquelle disparaissaient ces deux substances était la même (80% en 1 heure). Quand le Marsilid était donné six heures avant la réserpine et que les mêmes déterminations étaient répétées, la destruction des deux composés était presque complètement bloquée.

De manière à étudier les rapports entre l'action du Marsilid comme inhibiteur de la monoamine-oxydase ainsi que ses effets antidépressifs, cliniquement observés chez l'homme, le Marsilid a été donné au lapin et les variations de la teneur du cerveau en sérotonine et en noradrénaline ont été déterminées. Une seule dose élevée de Marsilid provoquait une élévation marquée de ces deux substances. Quand le Marsilid était donné à doses plus faibles, mais répétées, la concentration de la sérotonine et de la noradrénaline s'élevait lentement et atteignait le double de sa valeur normale en deux ou trois jours. Les effets secondaires comprenaient la mydriase et l'hyperexcitabilité. Il apparaît donc que les effets pharmacologiques du Marsilid sont temporairement en relation avec une élévation de la concentration des amines du cerveau.

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The Effect of Iproniazid on the Inactivation of Norepinephrine in the Human

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Circulating epinephrine and norepinephrine occur in relatively low concentrations in the blood in the resting condition, but may be greatly increased in response to conditions of stress. These elevations of epinephrine and norepinephrine quickly return to the normal level when stress is removed.[1, 2] Infusion studies have shown that the elevation of circulating epinephrine and norepinephrine produced by intravenous infusion of these substances rapidly returns to preinfusion levels when the infusion is stopped.[3] The rapid disappearance of circulating catecholamines may be due either to storage or destruction in the tissues. Von Euler observed no increase in tissue catecholamine content following its infusion intravenously.[4] We observed no increase in the catecholamine content of the red blood cells of the adrenal veins in 5 dogs subjected to insulin-induced hypoglycemia and hemorrhagic shock. However, adrenal vein plasma catecholamine output in these same dogs was extremely high.

Inactivation of epinephrine and norepinephrine takes place in many tissues. The actual mechanisms by which these compounds are inactivated are not completely known; however, it is thought that they include esterification of the phenolic hydroxyl group, enzymatic oxidation, enzymatic deamination, and O-methylation. Esterification of catecholamines seems to be localized in the liver and in the intestinal mucosa.[5] It is believed by some to be a major pathway in inactivation of catecholamines. The great objection to this view is that in eviscerated animals catecholamines are still destroyed to a large extent.[6] Furthermore, after infusion, conjugated epinephrine and norepinephrine is found to be only 1 to 2 per cent of the infused amount.[7] *In vitro* enzymatic studies have demonstrated that epinephrine is inactivated by catechol oxidase, the indophenol oxidase-cytochrome system, pseudophenolases, adrenaline dehydrogenase, cyanide-insensitive enzyme system, and monoamine oxidase.

Catechol oxidase has not been found, and pseudophenolase has been found in human tissue by some but not by other observers. The remaining enzymes or enzyme complexes have been found in human tissue. Of these, the indophenol oxidase-cytochrome system and the cyanide-insensitive enzyme system are capable *in vitro* of oxidizing epinephrine and norepinephrine to adrenochrome. However, *in vivo*, especially in the presence of vitamin C, glutathione, and perhaps other amino acids, it is doubtful if they are capable of carrying out this oxidation. Further, Schayer et al, using labeled epinephrine and adrenochrome, found after injections of these compounds in rats that there was a dissimilar urinary

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chromatogram. This indicated to them that adrenochrome is not an epinephrine metabolite in the living organism.[8] Adrenaline dehydrogenase, found in human blood by Imazuimi, was thought by him to be important in the metabolism of epinephrine and norepinephrine, but this has not been confirmed.[9] Monoamine oxidase *in vitro* catalyzes the oxidative deamination of many amine compounds, producing methylamine and an aldehyde as the end products; it is considered by some to be an important mechanism for the metabolism of norepinephrine. Monoamine oxidase is found in significant amounts in liver, kidney tubules, intestinal mucosa, and brain, and in relatively small amounts in other organs and tissues.[10] The action of it *in vitro* and *in vivo* in the central nervous system can be effectively inhibited by iproniazid.[11–13] However, it has not been shown that iproniazid inhibits monoamine oxidase *in vivo* in tissues other than the central nervous system.

In order to determine the effect of iproniazid on norepinephrine metabolism, infusions of norepinephrine were given before and after iproniazid administration, and the physiologic effects, blood levels, and urine outputs of norepinephrine were determined.

METHODS

Ten normal men were selected for the study. Each subject was allowed to lie quietly until his pulse and blood pressure were stable. Then two 15 ml. blood specimens were drawn at five minute intervals for plasma epinephrine and norepinephrine control levels. Norepinephrine in 5 per cent glucose in water was infused intravenously at the rate of 10 μg./minute for 60 minutes. The pulse rate and blood pressure were recorded at intervals during and for one hour following the infusion. Fifteen ml. heparinized blood specimens for plasma epinephrine and norepinephrine were drawn at 10, 20, 40, and 60 minutes following the start of the infusion, and at 2, 5, 10, 20, and 40 minutes after the infusion was stopped. The blood was immediately centrifuged, and the plasma was removed and frozen.

Twenty-four hour urine specimens were collected on the day of the infusion in 5 subjects. The urine was collected in bottles containing 15 to 20 ml. of 6 N hydrochloric acid and was refrigerated until the epinephrine and norepinephrine assays were made. Iproniazid (Marsilid)* was then given to each subject in the dose of 10 mg./Kg. of body weight/day for two days, and the entire infusion procedure and the urine collection were repeated. The infusion was started approximately two hours after the last dose of iproniazid.

The method of Weil-Malherbe and Bone,[14] as modified by Aronow,[15] was used for determination of epinephrine and norepinephrine in plasma. The method of von Euler and Floding, as modified by ourselves, was used for the determination of epinephrine and norepinephrine in urine.[16] These modifications included washing the acid eluate containing the catechols with two 4 ml. aliquots of *n*-butanol, which had previously been purified by washing with 0.1 N sodium hydroxide, 0.1 N hydrochloric acid, and distilled water. A standard solution of norepinephrine was made up in .25 N sulfuric acid. The acid had been treated previously with aluminum oxide. All specimens were centrifuged immediately before fluorescence was determined.

* The trade name of Hoffmann-La Roche, Inc. for iproniazid is Marsilid. Iproniazid as the phosphate salt, which was used in this study, was supplied by Dr. William Davis of Hoffmann-La Roche, Inc.

RESULTS

The effects of infused norepinephrine on the pulse rate, and the systolic and diastolic blood pressure before and after treatment with iproniazid are shown in table I and figure 1. They represent average values obtained for each subject during the sixty minutes of the experiment. It is readily apparent that the same magnitude of fall in pulse rate after norepinephrine infusion was found in the control subject as was observed in the iproniazid-treated subject. Furthermore, no significant difference was observed in the blood pressure.

Table II shows the average epinephrine and norepinephrine plasma levels during the sixty minute infusion of norepinephrine prior to and after treatment with iproniazid. Before treatment with iproniazid, infused norepinephrine raised the mean plasma levels of norepinephrine of 10 subjects from 2.67 μg./liter of plasma to 4.4 μg./liter of plasma, an increase of 1.74 μg./liter. After treatment with iproniazid, the infusion raised the mean plasma level from 2.19 μg./liter to 4.9 μg./liter, an increase of 2.71 μg./liter, a difference that may possibly have slight significance. The plasma norepinephrine levels returned to control values or below in one to three minutes after the infusion was stopped. Mean plasma epinephrine levels showed no significant change during the infusion of norepinephrine either before or after treatment with iproniazid.

Free and conjugated epinephrine and norepinephrine excreted in the urine during the twenty-four hours beginning with and following infusion of norepinephrine, both before and after treatment with iproniazid, are shown in table III. Prior to iproniazid treatment, mean values for urinary norepinephrine were 15.92 μg./24 hours and 12.90 μg./24 hours for the free and conjugated fractions, respectively. Following treatment with iproniazid, the

TABLE I

Average Blood Pressure and Pulse Rate in Normal Subjects during Infusion Prior to and After Administration 10 mg./Kg. of Iproniazid

	Before Iproniazid				After Iproniazid			
	Control		During Norepinephrine Infusion		Control		During Norepinephrine Infusion	
Subject	Blood Pressure	Pulse	Blood Pressure	Pulse	Blood Pressure	Pulse	Blood Pressure	Pulse
R. C.	106/75	84	119/80	71	112/72	74	113/91	53
W. S.	115/80	68	131/90	54	122/70	84	136/87	60
F. R.	110/84	60	126/94	51	110/75	60	128/87	49
F. M.	108/68	64	131/75	55	118/76	56	136/91	49
S. Z.	100/72	78	108/78	59	94/64	76	111/74	68
S. K.	106/78	64	133/86	44	129/88	70	141/91	52
W. W.	118/60	80	130/76	52	112/60	76	130/71	54
J. F.	110/64	74	119/80	55	118/56	80	142/93	57
V. P.	108/70	104	133/80	70	122/80	80	136/92	76
J. M.	112/80	80	123/93	46	124/76	88	143/94	51
Mean	109/75	76	125/84	56	116/72	76	134/87	57

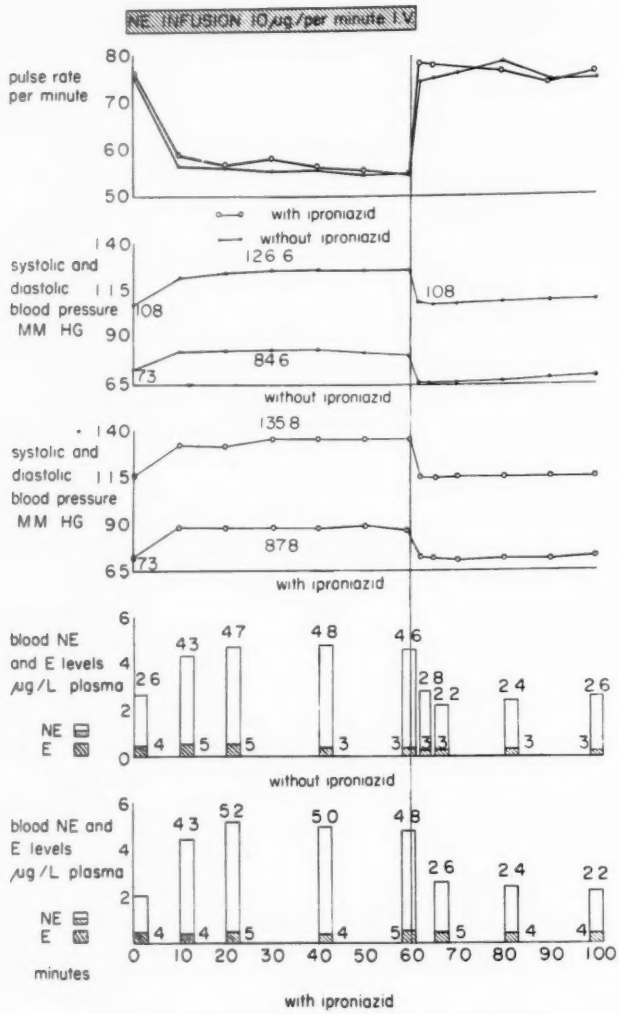

FIGURE 1

INFUSION OF NE BEFORE AND AFTER IPRONIAZID

free form decreased to 11.10 µg./24 hours, whereas the conjugated form rose to 26.98 µg./24 hours. Mean free and conjugated urinary epinephrine values were 3.08 and 0.56 µg./24 hours before, and 4.44 and 2.38 µg./24 hours after treatment with iproniazid.

In 5 subjects, studies were carried out to determine the percentage of infused norepi-

nephrine excreted in the urine (table III). Mean control values for free and conjugated norepinephrine excreted during the twenty-four hours preceding the infusion were 7.06 μg./24 hours and 8.36 μg./24 hours, respectively. Following the infusion of 10 μg./minute of norepinephrine for sixty minutes, the free norepinephrine excreted in the urine was 15.92 μg./24 hours and the conjugated norepinephrine 12.98 μg./24 hours. After treatment with iproniazid, free urinary norepinephrine values were 11.10 μg./24 hours and conjugated norepinephrine 26.98 μg./24 hours. Before treatment with iproniazid 1.47 per cent of the infused norepinephrine was excreted in the free form and 0.76 per cent in the conjugated form, thereby accounting for 2.23 per cent of the infused norepinephrine. Following treatment with iproniazid, a total of 3.77 per cent of the infused norepinephrine was excreted in the urine, 0.67 per cent as free norepinephrine and 3.1 per cent in the conjugated form.

The only important effect noted after administration of iproniazid was mild euphoria in 8 of the 10 subjects. There was a definite increase in physical activity and talkativeness, an inability to concentrate, and a general feeling of increased excitement. These effects were definitely accentuated by the infusion of norepinephrine in 5 subjects. In 2 persons no psychologic effect was noticeable from iproniazid, or from the norepinephrine infusion after iproniazid administration.

COMMENTS

If monoamine oxidase plays an important role in inactivation of norepinephrine in human beings, inhibition of the enzyme by iproniazid would be expected to result in potentiation

TABLE II

Plasma Norepinephrine and Epinephrine Levels during Norepinephrine Infusion Before and After Administration of 10 mg./Kg. of Iproniazid

	Before Iproniazid				After Iproniazid			
	Control		During Norepinephrine Infusion		Control		During Norepinephrine Infusion	
Subject	Norepinephrine (μg./liter)	Epinephrine (μg./liter)	Norepinephrine (μg./liter)	Epinephrine (μg./liter)	Norepinephrine (μg./liter)	Epinephrine (μg./liter)	Norepinephrine (μg./liter)	Epinephrine (μg./liter)
R. C.	2.2	1.1	4.7	1.1	1.3	0.0	6.2	0.1
W. S.	3.6	0.2	5.2	0.2	2.6	0.8	4.6	0.8
F. R.	2.7	0.3	3.6	0.2	2.7	0.2	6.2	0.4
F. M.	1.5	0.4	3.3	0.1	3.5	0.5	4.8	0.3
S. Z.	1.0	0.1	2.3	0.2	2.7	0.2	4.7	0.6
S. K.	1.3	0.1	5.0	0.1	1.0	0.9	3.8	0.2
W. W.	4.4	0.0	5.7	0.0	1.9	0.2	5.1	0.3
J. F.	2.7	0.0	4.5	0.4	1.7	0.6	4.5	0.8
V. P.	3.5	0.6	5.6	0.5	2.5	1.1	3.9	1.0
J. M.	3.8	1.3	4.1	1.6	2.0	0.0	5.3	0.3
Mean	2.7	0.4	4.4	0.4	2.2	0.5	4.9	0.5

of norepinephrine, with subsequent increased physiologic effects, higher blood plasma levels, and increased urinary output, especially following an infusion of norepinephrine. The results of this study failed to show any significant effect of iproniazid on either the physiologic action or the blood plasma levels of infused norepinephrine in normal human subjects. Control values of norepinephrine and epinephrine before and after treatment with iproniazid also showed no significant change, thus indicating that iproniazid did not influence endogenous catecholamine. Not only was there no significant potentiation of the physiologic effects or blood levels by iproniazid, but there also was no prolongation of these effects, and the elevated blood levels produced by infused norepinephrine fell to normal as quickly after treatment with iproniazid as after the control infusion.

The excretion of norepinephrine in the urine before and after treatment with iproniazid shows an apparent increase in the conjugated form of norepinephrine after treatment with the drug. This finding suggests that iproniazid may interfere with the inactivation of norepinephrine in human beings, which is compensated for by an augmentation of conjugation.

Recently it has been shown that the amount of methoxyepinephrine, a metabolite of epinephrine excreted in the urine of rats, is markedly elevated after administration of iproniazid followed by infusion of epinephrine.[17] The same mechanism is probably true for norepinephrine. Other inactivation mechanisms, whose end products are also not detected by the present urinary determination for free and conjugated norepinephrine, may also be accelerated by iproniazid.

It has been shown by several workers that only a small percentage of an infused amount of norepinephrine can be recovered in the urine.[7] In five control infusion studies, only

TABLE III

Recovery in the Urine of Intravenously Infused Norepinephrine Before and After Administration of 10 mg./Kg. of Iproniazid*

	Control				Norepinephrine Infusion Before Iproniazid				Norepinephrine Infusion After Iproniazid			
	Free		Conjugated		Free		Conjugated		Free		Conjugated	
Subject	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
W. S.	7.5	3.8	16.5	2.6	35.0	6.0	22.0	0.0	28.2	8.4	23.	0.0
J. M.	11.6	1.8	5.4	1.7	11.9	1.6	26.6	0.0	9.5	2.1	41.2	4.4
F. R.	7.2	0.8	9.0	1.2	11.0	2.0	12.0	0.5	4.2	3.0	33.9	0.0
S. Z.	7.0	2.0	4.9	1.8	15.3	2.9	0.0	0.7	10.8	7.7	15.7	0.7
J. F.	2.0	4.8	6.0	0.0	6.4	2.9	4.3	1.6	2.8	1.0	20.5	6.8
Mean	7.06	2.64	8.36	1.46	15.92	3.08	12.98	0.56	11.10	4.44	26.98	2.38
Recovery of infused norepinephrine					1.47%		0.76%		0.67%		3.1%	

* 10 μg./minute for 60 minutes.

2.23 per cent of the infused norepinephrine was recovered. After treatment with iproniazid, 3.77 per cent of the infused norepinephrine was found in the urine. This increase is accounted for mainly by an increase in the conjugated norepinephrine in the urine. This finding is further indication that iproniazid leads to increased inactivation of the infused norepinephrine by conjugation.

The euphorogenic action of iproniazid is of interest. In 8 of the 10 subjects euphoria developed with increased activity and talkativeness. This effect was accentuated in 5 of them by infusion of norepinephrine. This finding suggests that norepinephrine may act as a neurohumoral agent in the brain. Recently, Udenfriend et al, in studies on the effect of iproniazid on serotonin metabolism *in vivo*, showed that iproniazid had little or no effect on the peripheral metabolism of serotonin, but apparently did affect metabolism in the brain.[18] Our results suggest that this may also be true in the case of norepinephrine.

SUMMARY

Blood pressure, pulse rate, and plasma epinephrine and norepinephrine levels were determined in 10 normal subjects during infusion of norepinephrine (10 μg./minute for 60 minutes) before and after administration of iproniazid (10 mg./Kg.). No significant change was noted in either the physiologic effects or the blood levels of infused norepinephrine after administration of iproniazid.

In 5 subjects, determination of urinary norepinephrine showed an increase in norepinephrine excreted in the conjugated form after administration of iproniazid.

In 8 of the 10 subjects euphoria developed with increased activity and talkativeness after administration of iproniazid. This effect was accentuated by infusion of norepinephrine in 5 subjects.

RESUME

Les auteurs ont déterminé la tension artérielle, la vitesse du pouls et la concentration plasmatique de l'adrénaline et de la noradrénaline chez dix sujets normaux pendant la perfusion de noradrénaline (10 mg. par minute pendant soixante minutes), avant et après l'administration de 10 mg./kg. (d'iproniazide). A la suite de l'administration d'iproniazide, ils n'observèrent aucune variation appréciable des effets physiologiques ou de la concentration sanguine de la noradrénaline perfusée.

Chez 5 sujets la détermination de la noradrénaline urinaire a révélé une augmentation de la noradrénaline excrétée sous forme conjugée après l'administration d'iproniazide: Chez 8 de ces 10 sujets, l'euphorie avec hyperactivité et volubilité se sont manifestées après l'administration d'iproniazide; chez 5 malades la perfusion de noradrénaline accentuait ces réactions.

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Discussion

Chairman Udenfriend: I think it is becoming apparent that one of the things that Marsilid is doing is making it possible to uncover alternate important routes of metabolism of these amines. Recently Dr. Armstrong has shown the methoxymetabolite, 5-hydroxytryptamine, of norepinephrine in the urine, and many workers have become involved in studying the biosynthesis. The most important and, I think, the most interesting work has come from the laboratory of Dr. Julius Axelrod, who will discuss this important route of metabolism for a short time, and will also try to indicate its importance in the handling of exogenously and endogenously administered norepinephrine.

Dr. Julius Axelrod:* For the past 20 years, the catecholamines were considered to be metabolized by monoamine oxidase. However, Dr. Friend's report and the reports of other investigators suggest that these catecholamines are metabolized by pathways other than deamination.

Recently Armstrong found that patients with pheochromocytomas showed a marked increase in the excretion of 3-methoxy-4-hydroxymandelic acid. This fact suggested to us that this increase may arise by two pathways; one pathway, favored by Armstrong, is deamination of the catecholamines followed by methylation, and another is methylation

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TABLE I

*Enzymatic O-Methylation of Epinephrine**

Additions	l-Epinephrine Metabolized (μM)
None	0.00
S-adenosylmethionine (0.05 μmole)	0.04
S-adenosylmethionine (0.1 μmole)	0.07
Magnesium chloride omitted	0.02

* Soluble supernatant from rat liver (10 mg.) incubated with 0.1 μM of *l*-epinephrine, *p*H 7.4 buffer, and magnesium chloride for thirty minutes at 37 C.

of the catecholamines followed by deamination. In subsequent work, we found Marsilid to be a powerful tool in elucidating the mechanism and the pathways of the metabolism of the catecholamines.

We approached the problem at the cellular level. It has been known that nitrogen could be methylated by S-adenosylmethionine, methionine acting as a methyl donor. We thought that a similar mechanism would operate in the methylation of oxygen groups. This possibility was examined in the following experiment.

When rat liver soluble supernate fraction was incubated with *l*-epinephrine *d*-bitartrate, we found that practically none of the epinephrine disappeared (table I). However, when S-adenosylmethionine was added, we found a considerable amount of the epinephrine metabolized. Magnesium ions were required for this reaction. This metabolic product did not have a catechol reaction, indicating that one of the phenols was presumably methylated. A possible product could be 3-methoxy-4-hydroxyepinephrine, which we shall call hereafter "metanephrine."

We did not have any authentic metanephrine on hand at the time. However, 3-methoxy-4-hydroxymandelic acid was available. When we incubated the metabolic product with a monoamine oxidase preparation, we found that the resulting product was identical with that of 3-methyl-4-hydroxymandelic acid, indicating the methylation had occurred on position 3.

Subsequently, Drs. Witkop and Senoh, at our institute, synthesized authentic metanephrine, and we found it to be identical with the enzymatically formed methylated product.

Table II shows the distribution of this enzyme. It is fairly widely distributed in the kidney, spleen, small intestines, lung, and brain. However, there is no activity in heart and skeletal muscle. It is present, however, where catecholamines are found and exert their action. We have found the enzyme present in all mammalian species examined, including man.

We also studied the substrate specificity. Only compounds with a catechol nucleus were methylated. None of the monophenolic compounds could be methylated. The enzyme was purified some thirtyfold. With the purified enzymes, in order for methylation to occur, a divalent metal had to be present. The enzyme was inhibited by sulfhydryl binding agents,

TABLE II

Tissue Distribution of O-Methylating Enzyme

Tissue	Relative Activity (%)
Liver	100
Kidney	14
Spleen	7
Brain	6

indicating that the divalent metal hooked onto the two phenolic groups of the catechols, which in turn attached the catechol onto the sulfhydryl group of the enzyme.

Our next problem was to find out whether or not the particular reaction was operating in the intact animal. In rat urine, we found both normetanephrine and metanephrine normally present in the form of a glucuronide.

After administering epinephrine, we isolated a compound from the urine that had the same R_f as metanephrine. After administration of norepinephrine, we found excreted a compound that had the same R_f as normetanephrine. Upon administration of the 3-methoxy dihydroxyphenylalanine amine, we found 3-methoxytyramine excreted.

After the administration of *l*-epinephrine, approximately 3 per cent of the epinephrine was excreted as a metanephrine, and 22 per cent as metanephrine glucuronide, a total of 25 per cent being excreted (table III). The 25 per cent excreted could represent only a minimal amount of methylation that actually occurred, since the methylated compound could, in turn, be metabolized further.

We administered the metanephrine to the rat and found that approximately 34 per cent was excreted unchanged or as the glucuronide, indicating that approximately 65 per cent of metanephrine that is formed from epinephrine would have undergone further metabolism.

In order to determine the further metabolic route of metanephrine, we used Marsilid, a monoamine oxidase inhibitor. It was found that the excretion of the metanephrine was more than doubled, indicating the metanephrine formed is, in turn, deaminated by monoamine oxidase. After administration of metanephrine and Marsilid, the excretion of metanephrine is doubled. Essentially the same result was found after the administration of norepinephrine (table IV).

TABLE III

O-Methylation of Epinephrine in the Rat

Drug Administered	Free Metanephrine (%)	Metanephrine Glucuronide (%)	Total (%)
l-Epinephrine	3	22	25
dl-Metanephrine	8	26	34
l-Epinephrine and Marsilid	4	51	55
dl-Metanephrine and Marsilid	10	59	69

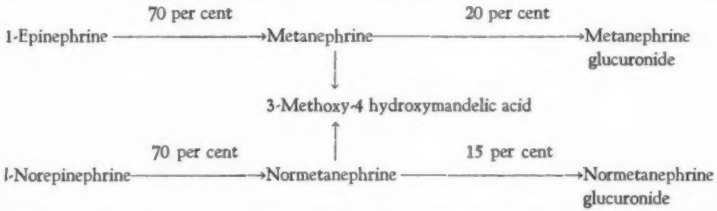
TABLE IV

Metabolic Fate of Norepinephrine

Drug Administered	Methoxynorepinephrine (%)	Methoxynorepinephrine Glucuronide (%)	Total (%)
l-Norepinephrine	3	14	17
dl-Normetanephrine	12	13	25
l-Norepinephrine and Marsilid	3	27	30
dl-Normetanephrine and Marsilid	21	27	48

TABLE V

Proposed Pathway for Metabolism of l-Epinephrine and l-Norepinephrine in the Rat



These observations suggest the following pathway for the metabolism of catecholamines (table V). Approximately 70 per cent of epinephrine and norepinephrine are methylated on a 3-hydroxy position, 15 to 20 per cent of which is further metabolized by glucuronide formation. The enzyme that converts metanephrine to the glucuronide is localized in the microsome of the liver and requires a uridine diphosphate glucuronic acid as the glucuronic acid donor. A considerable part is deaminated, presumably to form 3-methoxy-4-hydroxy-mandelic acid.

We looked for these compounds in the brain of the rat, and found by our methods that we could not detect metanephrine or normetanephrine. Upon administration of Marsilid, however, we found a compound in the brain that had the same R_f as norepinephrine.

We also found both metanephrine and normetaphrine in the adrenal glands of the Marsilid-treated animals. Dr. Sjoerdsma has also found normetanephrine in pheochromocytomas. Barger and Dale have shown that numerous sympathomimetic amines, related in structure to epinephrine, have physiologic activity. It is possible that some of the action of the catecholamines, epinephrine, or norepinephrine may be mediated through their methylated products.

Clinical Experience with Iproniazid (Marsilid)

*Nathan S. Kline, M.D.**

ORANGEBURG, NEW YORK, AND NEW YORK, NEW YORK

The stone which the builder
rejected is become the chief cornerstone
Psalms 118:22

The reinvestigation of iproniazid (Marsilid)† after it had previously been rejected[1, 2] for psychiatric use provides an illustration of the necessity for continued collaborative effort between those whose specialized training is in psychiatry and those whose specialized training is in biochemistry and pharmacology.

In an effort to follow the possible mode of action of reserpine and its effect on serotonin, norepinephrine, and other substances, it had been found that, by giving the animal prior doses of iproniazid, reserpine instead of acting as a sedative seemed to bring about heightened awareness and activity.[3, 4] Since my interests are not primarily pharmacologic, I was most impressed by the clinical state of these animals, and the possibility of treating withdrawn and depressed patients occurred to me. I discussed the matter with a colleague and collaborator‡ who suggested that the amine oxidase inhibition induced by this drug[5] might be crucial to the state of heightened awareness. The ward on which the original hospital study was done was selected because the physician then in charge§ had inquired whether we had any drugs with which to treat apathetic and depressed patients. These results have been reported elsewhere.[6]

Concomitantly, iproniazid was used in the treatment of depressed and lethargic patients seen in my private psychiatric practice. Success was evident in a high percentage of patients from the very beginning. The first two private patients given treatment (started well over a year ago) manifested one of the anomalies found with the use of almost all the psychopharmaceuticals, namely, that some of the patients require maintenance doses and others do not. One patient, a young married woman in her thirties, was able to break through a depression that had withstood some seven years of psychoanalysis plus two years on assorted tranquilizing drugs. After a few months of treatment, severe neuralgia of the throat and both ears developed. The patient insisted that, even if the excruciating pain were to continue the rest of her life, she preferred it to the emotional and mental anguish she had been suffering. It was explained that the action of the drug probably persisted for some time after its withdrawal, and that temporary stoppage plus vitamin B_6 would prob-

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§ Dr. Harry P. Loomer, Supervising Psychiatrist, Rockland State Hospital, Orangeburg, New York.

ably clear up the neuralgia so that medication could be reinstituted before the depression recurred. As things worked out, medication was never restarted and, in contrast to her former pattern of living, which consisted of going back to bed immediately after her husband and children had gone to work or to school, she is now caring for her household efficiently and doing full time graduate work in preparation for a professional career.

The other patient, a trained baby nurse, had originally been referred by an internist to whom she had gone for treatment of somatic complaints. He was concerned with the suicidal risk she presented. She had undergone prolonged psychiatric treatment in the past without any real effect. Her pattern of living consisted of caring for a newborn infant a few weeks after its discharge from the hospital, a period of unemployment while she waited for a new position of this type, and then a repetition of this pattern. Despite offers of more prolonged employment, she was either too restless or fearful of developing a more prolonged relationship. Her response to iproniazid was immediate and dramatic. Even her physical appearance changed. The scowling brow and the drawn mouth were replaced by a relaxed and smiling appearance, which incidentally made her look twenty years younger. This patient after a year of therapy has now accepted steady employment and is gradually constructing for herself the beginning of an adequate social life. The continuous headaches, for which she was taking from 15 to 20 aspirin a day, have now been virtually eliminated and, although she will probably require prolonged psychotherapy, she now appears capable of responding to this. During the past year on a number of occasions medication with iproniazid was discontinued or lowered to 10 mg./day. On each of these occasions the depression recurred within approximately one week. It appears, therefore, in contrast to the first patient, that a continuous maintenance dose is essential in this patient.

Another patient whom I treated unsuccessfully with tranquilizers for well over a year is now being handled successfully by a general practitioner to whom I act as consultant. In this patient also, as soon as dosage drops below 35 mg./day, there is a recurrence of symptoms. It is of extreme interest that the first patient and the one just referred to had obsessive thinking as the most marked feature. In two other cases of obsession the patients were successfully treated, which raises the question as to whether or not there might be depression underlying most cases of obsession. Only 1 compulsive patient has been treated with iproniazid by me in private practice and this was recently. The anxiety and panic accompanying the compulsions disappeared within a few weeks, but even after two months of treatment there has been no marked change in the compulsive behavior *per se*. There appears to be some evidence that despite certain superficial similarities the obsessives and the compulsives should not be classified in a single grouping. Pharmaceutical response may thus be of great value in determining psychodynamic action and cause.

The use of iproniazid in psychoanalytic therapy had already been initiated at the time of our presentation[6] in April 1957 and was more fully documented at the second presentation[7] given before the Society for Biological Psychiatry in June 1957. At that time a series of cases by a variety of therapists were included and particular notation made of the finding by H. Spiegel that the combination of an amphetamine with iproniazid appeared to act synergistically to expedite the reaction.

I would like to refer to a manuscript being prepared by Ostow, who has now treated 8 patients with iproniazid. He carefully reviews the case history of an analysand whom he saw for 144 sessions. To quote directly: "Several questions present themselves. First, was it wise to complicate and (as it turned out) shorten the analysis by administering Marsilid? I can well imagine that the patient might have begun to come out of his depression within a few days, weeks or months even without the drug. However at the time it was given, he had not, and the analysis was then threatened by three hazards, suicide, business failure and premature termination. These hazards were overcome by the use of the drug." Ostow also discusses the greater desirability of more analytic work. "In fact, if Marsilid can relieve depression, why should it not replace analysis rather than merely supplement it? The answer, of course, lies in the goal of therapy. If one is interested, as the nonanalytic psychiatrist generally is, in relieving an acute episode of illness, Marsilid can be used as electroshock is now being used. This, however, is not the goal of the analyst. He sees an episode of depression . . . as merely a phasically recurrent symptom in a sick personality. In other words, for the analyst, the depression is not the illness. The personality in which the depression appears is a sick one, and it requires treatment as much in symptom-free intervals as during the depressive episode. Although it is usually the depression which brings the patient for treatment . . . the analyst will attempt to see the total problem. If the patient satisfies the usual criteria for analysis he will recommend analysis. In other cases, the patient will be referred for one of the symptomatic therapies, hitherto shock, and now probably Marsilid."

On the basis of the relatively small number of patients he has in analysis he believes that it is too early to offer a definite metapsychologic hypothesis, but he definitely does believe "the patient becomes more eager for object relations than hitherto. Libidinal strivings become more active, and to the extent that they find a suitable object, the patient loses his feeling of depression. Where satisfactory external objects are not available, narcissistic libidinal investment becomes gratifying too." He notes later, "to a certain extent therefore even when objects are not available the drug makes it possible for the individual to advance from the point where his only intrapsychic objects are images of the self and the unconscious to the point where he can cathect pre-conscious images of the self and external objects. How this is done I do not know. One possibility is that the drug makes more libidinal energy available to the ego thereby permitting the ego to reach out actively for object ties and at the same time making the narcissistic cathexis pleasurable rather than painful." This in essence is an equivalent statement, in metapsychologic terms, that iproniazid appears to act by supplying or mobilizing psychic energy.

Also of considerable interest is the patient addicted to alcohol who was treated by Ostow and in whom results appear to have been quite successful. He quotes a personal communication from Nunberg who says that he "considers periodic drinking to be essentially a manifestation of depression, and addiction in general, including addiction to alcohol, to be an expression of depressive illness." On purely empiric grounds, Bosworth had predicted the possibility of the use of iproniazid in narcotic addiction, and 2 cases have come to my attention in which this treatment appears to have been successfully employed.

Although it is undoubtedly true that episodes of depression or anxiety are merely episodic transactions of certain personalities with their environment, it also appears to me that in many and probably most instances there are tremendous reservoirs of self healing. The removal of depression and/or anxiety, which like pain may interfere with the self curative processes, is a legitimate medical function. This certainly justifies the use of iproniazid by the general practitioner who, by relieving the acute symptoms of depression or lethargy and possibly certain types of anxiety and obsession, may set the stage for the individual to complete the healing process himself. In other persons psychiatric guidance and therapy is required, and probably in still others treatment aimed at modifying the personality structure (for example, psychoanalysis) is the treatment of choice. The general practitioner who does not obtain this satisfactory response in one to two months should do as he does in other areas of medical practice and seek the advice and guidance of a specialist.

The selective action of various psychopharmaceuticals now at our disposal is sometimes quite amazing. Earlier this year I saw a fairly well known young artist who had been unable to produce any new canvases for over a year. Treatment with iproniazid seemed to "break the dam," and during the summer he produced a profusion of oil paintings, water colors, and sketches totaling more than a hundred. There remained, however, a residue of anxiety and hostility, which subsided only when prochlorperazine* was added to the treatment.

An almost parallel case was that of a patient in the television industry in whom iproniazid relieved the depression but did not touch the anxiety. Discontinuance of iproniazid brought with it a return of the depression, and recommencement of the drug led to alleviation once again. It was necessary to utilize one of the phenothiazine derivatives to relieve the anxieties sufficiently for the patient to receive enough relief from the symptoms to become at all amenable to psychotherapeutic influences. It should be glaringly evident that I believe strongly that there is no conflict between psychotherapeutic and pharmacotherapeutic techniques and that wherever it appears useful the two should be used in combination.

Like any potent drug, inevitably there are side effects, of which jaundice is probably the most serious, and continuing efforts will be made to find more potent and less toxic pharmaceuticals that have the same action. There is preliminary confirmation of the theory that action is by way of amine oxidase inhibition, both from the work of Brodie et al on iproniazid and other amine oxidase inhibitors, and from our own preliminary testing on human beings of a number of agents known to act in this matter. Whether these newer preparations possess a more favorable therapeutic index will not be known for some time but they do indicate that we appear to be on the right track.

In acute depression, high dosages (50 mg. three times a day) should be given initially in conjunction with 10 to 30 mg. of amphetamine cr an equivalent psychomotor stimulant. The patient should be warned of possible side effects but unless these are very marked the dose should be continued until there is a therapeutic response. Treatment with lower doses takes much longer or is not effective at times. As soon as evidence of therapeutic

* The trade name of Smith, Kline & French Laboratories for prochlorperazine is Compazine.

response has been obtained the dosage should be dropped to between 10 and 25 mg./day and continued for one week. If symptoms recur the dosage should be raised; if symptoms do not recur the dosage should be lowered until a maintenance level is established. After one or two months a further trial may be made to reduce the dosage level. Unfortunately many psychiatric patients either try to prove that they "can be well by themselves" and stop all medication by their own prescription, or they are reluctant to reduce the dosage even when indicated and have to be fought down the scale milligram by milligram. In the former category is a housewife who has now had seven remissions and seven exacerbations, each related to the patient's decision that she was so well she no longer needed medication. In the latter category is a professor of medicine in a well known university who, despite annoying side effects, cannot be persuaded to reduce the dose of iproniazid below 75 mg., since he would "rather suffer the side effects" and be free of the depression that has plagued him for twelve years than "take any chances."

In the milder cases commensurate lower doses can be used but the same treatment principles are recommended. Probably a minimum of 25 mg. three times a day should be the starting dose. When insomnia is annoying, this can then be reduced by omission of the evening dose.

In the cases already described no effort to provide statistical validation was made. In previous papers[6–8] we have made a beginning toward this with respect to hospitalized patients and a number of private practitioners, such as Sandler, Furst, and Robie have extensive series which have been or shortly will be reported on. At a recent meeting of the New Jersey Neuropsychiatric Association, Furst, reporting on a series of 100 depressed patients said "approximately three out of every four endogenously depressed patients respond as well, if not better, than with electroshock therapy." Robie stated, "I couldn't believe we had found a drug that would bring people out of depression without electroshock therapy, but I had to eat my words because I have proven it to myself without the slightest question in the past six months." Sandler, who was among the first private practitioners of psychiatry to use iproniazid, has already been quoted extensively in our previous papers and is recognized again for his early confirmation of our claims.

The cases presented were mentioned to illustrate specific points of dosage, regimen, or response. Obviously not all indications could be illustrated by case histories, and reference should be made to cases of anxiety states and to early schizophrenics in whom the treatment was combined with either phenothiazines or reserpine. In a case of mental deficiency complicated by anorexia nervosa, the results were dramatic. Reference has been made to the use in alcoholism and drug addiction. In some elderly persons with depression and loss of interest the results have been quite satisfactory.

Having experimented with iproniazid on myself for a few weeks I found that it did not produce the usual letdown that follows the use of the psychomotor stimulants; also the usual motor tenseness and excitation were absent. As one of my colleagues so effectively put it, "Psychomotor stimulants speed up the pumps—Marsilid fills them." Instead of the sleeplessness, which is a usual accompaniment of the psychomotor stimulants, I found sleep to be essentially normal but of markedly shorter duration than usual. All of these

findings have been confirmed in various patients and some of them have had as little as three to four hours sleep per night for a year. Patients should be warned to expect this as it frequently proves quite disturbing. Mention should also be made of the possibility of constipation, delayed micturition, and possible impotence, although sometimes the opposite results are obtained. During the period when I was receiving the medication, judging subjectively (and my secretary judging objectively), my efficiency rather than falling off was increased.

At present we are designing an experiment to determine how iproniazid affects the performance of essentially "normal" persons who are called upon for intense functioning over fairly sustained periods. It is certainly not only feasible but desirable to determine if there are chemicals that could improve ordinary performance. Iproniazid may constitute a "front-runner" for such medications. Certainly it differs greatly enough from the psychomotor stimulants to require a new category, which we have called "psychic energizers," and it is entirely possible that the beneficial action may not be limited to sick persons with obvious deficits. Just one hundred years ago, when anesthesia was introduced, it was objected that it was "unnatural" since people had always suffered pain during any operative procedure or during childbirth. If it is found that there are pharmaceuticals that will intensify and improve certain human functions, undoubtedly the same cry of "it's not natural" will be raised. It is characteristic of man that he wanted to fly through the air and now into outer space, to travel under water, to communicate through thousands of miles instantaneously, and to do all matter of things. It is the most "natural" of characteristics that man should attempt what is unnatural, unbelievable, or impossible and succeed.

RESUME

Quand, en clientèle privée, le Docteur Kline a administré l'iproniazide à ses malades dé primés, "le succès a été évident dès le début dans un pourcentage élevé des cas." Dans plusieurs cas, où l'affection durait depuis longtemps, les malades ont répondu au traitement de façon spectaculaire. Le Dr. Kline signale qu'étant donné l'action favorable de l'iproniazide dans les phases aiguës de l'affection il peut remplacer l'électrochoc-thérapie.

L'auteur déclare que chez les malades en état de dépression aiguë, il faut administrer une dose élevée (50 mg. trois fois par jour), plus 10 à 30 mg. d'amphétamine. Sauf en présence de réactions secondaires marquées cet auteur préconise l'emploi de cette dose jusqu'à ce que la réponse au traitement ait été obtenue. La dose d'iproniazide doit alors être réduite de 10 à 25 mg. par jour. Si les symptômes réapparaissaient, la dose devrait être augmentée. Au bout d'un mois ou deux, il y a lieu de tenter une nouvelle réduction de la posologie. Dans les cas où la dépression est moins marquée, l'auteur suggère d'administrer 25 mg. trois fois par jour pour commencer.

Le Dr. Kline considère que les médecins praticiens apprécieront l'utilité de l'iproniazide pour supprimer les symptômes aigus de la dépression. Néanmoins, si une réponse favorable n'a pas été obtenue au bout d'un mois ou deux, il y a lieu de consulter un spécialiste. En se fondant sur son expérience personnelle, l'auteur soulève la question de la valeur ou non valeur de l'iproniazide pour améliorer l'efficience chez l'individu normal.

Ainsi que d'autres chercheurs, Kline prévient les médecins d'avoir à surveiller l'apparition de signes d'ictère, de constipation, de dysurie et peut être d'impuissance.

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Discussion

Dr. George Crane:* Marsilid was initially heralded in the lay press as the drug that permitted bedridden tuberculous patients to dance and sing in their wards. It later became known as an energizer capable of producing unlimited resistance to fatigue. However, if one places too much emphasis on these spectacular reactions, which are not always desirable, one runs the risk of overlooking other pharmacologic effects of greater therapeutic value and theoretical interest.

When I first introduced Marsilid in my private practice, I was most reluctant to use it in compulsive, hard driving, and overambitious individuals for fear of increasing these trends and creating a dangerous manic condition. This apprehension proved to be unfounded because calmness and contentment, and not overactivity, developed in a number of patients during certain stages of treatment. This is illustrated by the following case.

A man in his middle forties who had tried to prove to his superior, to his subordinates, and to himself that he was the most efficient worker in the organization, sought psychiatric help, since he could no longer endure the pressure of work. He was given a daily dose of

* Montefiore Hospital, Bronx, New York.

100 mg. of Marsilid and after ten days of treatment reported that, for the first time in fifteen years, he could have his coffee breaks and engage in casual conversation with his co-workers without fear of wasting his time. He accomplished this, not by shirking his responsibilities or by defying authority, but by becoming more interested in his work and his co-workers. Concomitantly, there was a change of attitude toward his family. Heretofore he appeared to have been happy only when he was alone. After he had been taking the drug for some time, he became affectionate with his wife and actively interested in his children.

This greater involvement with people and work is often associated with an increased sensitivity to outside stimulations. This increased contact with outside reality is paralleled by a greater awareness of inner feelings. Patients again experience the deep emotions that had not been available to them since their childhood. They become more spontaneous and more confident in their inner resources. They often cry profusely and then feel great relief from inner tensions and futile preoccupations. A patient who had been severely depressed for six months made the following statement in his second week of treatment: "I used to cry and feel miserable afterwards; now I cry more often, but I become sentimental." This is a remarkable statement from a patient who was emotionally depleted, plagued by phobias, and in poor contact with reality.

As long as the patients can maintain contact with their affective forces and receive sufficient stimulation from their environment, their mood remains adequate and their outlook is optimistic. However, symptoms and phobias do recur in some cases in spite of continued treatment. A possible explanation may be that a greater insight into one's personality may uncover simultaneously suppressed resources and severe neurotic limitations. Hostility, detachment, and inadequacy are experienced more intensely and therefore these trends clash with the more spontaneous feelings, such as love, compassion, and healthy assertiveness.

In conclusion, I believe that Marsilid is effective in facilitating the individual's receptivity to random stimulations from outer sources and, at the same time, in increasing the general input of inner sensations. For this reason, the drug is most valuable in the treatment of patients with phobic-obsessive neuroses and patients with depressions. The former are detached from reality by monotonous inner preoccupations and the latter by poor contact with themselves due to paucity of emotions. As the result of treatment with Marsilid, the patients become more alive and capable of more positive feelings toward other people. Last but not least, the therapist benefits from Marsilid in that his patients appreciate his therapeutic endeavors and therefore cooperate more effectively in the therapeutic situation.

Marsilid for Hospital Psychiatry

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This report deals with results that must be considered preliminary and inconclusive but they may indicate a direction for further investigation that could produce clinically significant results. Used as background material were the early reports of Dr. Kline and his co-workers and some observations of our own on the effect of isoniazid on a group of patients at a state hospital (table I).

Administration of Marsilid† to a few patients in the state hospital was begun early in the summer, but most of the work was done in the past three months. During this period, a group of private patients, some ambulatory and some hospitalized, were also treated with Marsilid. Some of the scientific determination of drug effects were carried out in an unorthodox manner, but long-term familiarity with the patients under various forms of treatment served as our base line for the two contrasting parts of this study.

The state hospital patients were chosen at first for their resistant immobility, withdrawal, and general inertia, without regard to diagnostic category or duration of illness. As a result, they represent a group of resistant, chronic psychotic persons, who could hardly be expected to improve under any circumstances. In these patients, however, some changes developed that must be analyzed further. To avoid delay in gathering data, patients who had been receiving any other drug over a period of time and who had received no particular benefit were given Marsilid in addition to the other drug. This form of control is complex but valid when the group under study is compared with a group receiving Marsilid alone, and with groups receiving other drugs. Since more than two thirds of the 3200 patients in the Longview State Hospital receive drugs of one kind or another, no new drug or combination of drugs can be said to represent a source of special attention.

The private patients comprised an entirely different group who, after a few preliminary observations were given what may be called desperation therapy. One man, 63 years of age. suffering from a recurrent anxiety state of probable involutional origin, had improved only slightly when treated with prochlorperazine.‡ Three years ago, electric shock therapy had improved his condition. However, he refused further electroconvulsive therapy. Marsilid was then given in addition to prochlorperazine. After two weeks the somatic complaints had subsided, and after one month the patient was more cheerful and outgoing than he had ever been. These results, as well as good results obtained with other patients, encouraged further observations in this group of private patients.

Adult patients were given 50 mg. of Marsilid three times a day. Frail or senile persons were given 25 mg. three times daily, which was increased after one or two weeks if the medication was well tolerated. All medication was given orally.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

‡ The trade name of Smith, Kline & French Laboratories for prochlorperazine is Compazine.

TABLE I

*Isonicotinic Acid Project**

Number treated	119
Number on control drug	45 (acetylsalicylic acid)
Men treated	59
Women treated	60
Dosage given	100 mg. twice a day
Electroencephalograms obtained	10 (not remarkable)
Electrocardiograms obtained	10 (not remarkable)
Basal metabolic rates obtained	10 (not remarkable)
Weight	No significant changes
Blood chemistry	No significant changes

* The project covered a twelve-week period from September to November 1952. The initial condition of four patients improved in significant ways, particularly in ability to communicate verbally, in diminution or absence of assaultiveness, incontinence, denudativeness, and other gross manifestations of psychosis; noted also was some diminution of psychopathologic manifestations, such as delusions and hallucinations, without actual resolution. One hundred and fifteen patients improved slightly or did not improve at all. The control subjects improved slightly or did not improve at all.

The results obtained in the state hospital patients, as compared with the private patients, appear in table II. The private group consisted chiefly of affective disorders. Even the schizophrenic patients in this group had been relieved of the schizophrenic manifestations and were treated for specific depressive anxiety. The state hospital group consisted chiefly of schizophrenic psychotic patients who were not actually depressed or anxious, but who were autistic and had already achieved what they had conceived to be their nirvana (table III).

It appears that Marsilid may act as a specific remedy in certain forms of depression and anxiety, as noted in table IV. Benefit from Marsilid sometimes begins after two or three

TABLE II

Results of Administration of Marsilid

	State Hospital Patients			Private Patients		
Condition	No. of Patients	Good Result	Bad or Worse	No. of Patients	Good Result	Bad or Worse
Schizophrenia	22	—	8	2	1	—
Affective disorders	8	1	2	19	11	1*
Psychoneurotic disorders	1	—	1*	11	2	—
Other disorders	2	—	1*	1	—	—
Total	33			33		

* Incomplete.

days of therapy, but it may not be manifest for several weeks. Of particular interest is the group of 11 patients specifically noted in table IV. All of these would formerly have been given electric shock treatment. With the use of Marsilid, electric shock treatment had become unnecessary in these patients.

The side effects of administration of Marsilid (table V) have not been frightening in these patients. Hypotension was the primary problem. It was sometimes associated with concurrent use of phenothiazine compounds, which do not by themselves cause hypo-

TABLE III

*Results in Patients Treated One Month or More with Marsilid**

19 Patients Treated with Marsilid Alone or with Another Drug						10 Patients Treated with Marsilid Alone					
Time Treated	A†	B‡	C§	D‖	E¶	Time Treated	A	B	C	D	E
0–6 months		1	2			0–6 months		1	1		
6 months to 2 years			2			6 months to 2 years					
2 to 5 years			4			2 to 5 years			1		
5 to 10 years			1	1		5 to 10 years					
Over 10 years			3	3	2	Over 10 years			3	3	1

14 Schizophrenic Patients Treated with Marsilid Alone or with Another Drug						7 Schizophrenic Patients Treated with Marsilid Alone					
Time Treated	A	B	C	D	E	Time Treated	A	B	C	D	E
0 to 6 months			1			0 to 6 months			1		
6 months to 2 years			1			6 months to 2 years					
2 to 5 years			4			2 to 5 years			1		
5 to 10 years			1	1		5 to 10 years					
Over 10 years			2	2	2	Over 10 years			2	2	1

* State hospital patients only.

† Patients who have recovered from all active psychotic manifestations, particularly with respect to delusions and hallucinations, who have insight into previous delusions and hallucinations, who have adequate affect and social and industrial adaptive capacity, and whose condition is equal at least to the premorbid level; they show no overt hostility to the hospital staff.

‡ Patients who have recovered from most psychotic manifestations but who may not have lost belief in previous delusional experience, who are able to make a satisfactory social and industrial adaptation away from the hospital or in the hospital under privileged conditions, and whose improvement may be summarized as "a good social remission."

§ Patients who have improved in significant ways, particularly in their ability to communicate verbally, in diminution or absence of assaultiveness, incontinence, denudativeness, and other gross manifestations of psychosis, and in some diminution of psychopathologic manifestations, such as delusions and hallucinations, without actual resolution.

‖ Patients who have improved slightly or not at all.

¶ Patients who became worse.

tension. Hypotension is apparently always orthostatic. Modification of dosage or temporary withholding of the drug is effective in ameliorating this symptom; both the phenothiazine and the Marsilid dosage should be diminished. When hypotension is severe or

TABLE IV

*Marsilid as Treatment for Certain Forms of Depression and Anxiety**

Patient	Diagnosis	Synergist	Previous Treatment	Results of Treatment
M. McG.	21.11†	Prochlorperazine	None	Relief in two days from depression of six months' duration
A. C.	21.11	Perphenazine	ECT, lobotomy	Depression and withdrawal; first relapse in over five years relieved within one week
J. R.	21.11	Prochlorperazine	ECT	Depression and anxiety of over one years' duration relieved in approximately four weeks; some tendency to (acceptable) hypomania
B. A.	21.11	Prochlorperazine	ECT	Depression of approximately one years' duration relieved in two to three weeks
E. S.	21.11	Prochlorperazine	ECT	Recurring depression subsided in approximately one week
R. H.	21.11	Prochlorperazine	ECT	Relapsing depression relieved in less than two weeks
G. G.	20.02	Prochlorperazine	ECT	Resistant depression of six months' duration relieved in approximately four weeks
J. K.	20.02	Prochlorperazine	None	Resistant depressive anxiety of one years' duration relieved in approximately four weeks
B. H.	20.01	Perphenazine	ECT	Relapsing depression in elderly woman over 70 relieved in approximately one month
C. S.	22.61	Perphenazine	ECT	Previous schizophrenic with acute depressive reaction responded in less than one week
J. S.	40.0	Perphenazine	None	Acute depressive anxiety relieved in less than one week

* Private patients only.

† Diagnostic categories in official (American Psychiatric Association and United States Bureau of Census) classification.

TABLE V

Side Effects of Marsilid

Effects	Total No. of Patients	Marsilid Alone
Hypotension	6	2
Weak	5	1
Dizzy	6	0
More psychotic	3	1
Became manic	1	1
More depressed	2	1

intractable, small doses of cortisone (12.5 mg. once or twice daily) or ACTH restores blood pressure to normal. Other side effects described by patients as weakness and dizziness are probably related to hypotension of transient duration. Investigation for possible cerebral dysrhythmia has given negative results. In none of the patients did any blood dyscrasia or liver damage develop. Some intolerance to small amounts of alcohol was noted in 2 private patients who suffered excruciating headaches the day following "one or two" drinks.

SUMMARY

We have observed definite benefit from the use of Marsilid in depressed and anxious patients. However, no benefits are obtained in the treatment of psychotic manifestations in chronic schizophrenic psychotic persons; possibly the condition is even accentuated. No attempt was made to interpret these preliminary findings, except perhaps to say that they lend further credence to the concept that an organic mechanism is an underlying factor in psychotic and related processes, and that schizophrenia and affective disorders probably have different underlying mechanisms.

RESUME

L'auteur rapporte que le Marsilid s'est révélé utile chez des malades déprimés ou anxieux, mais que dans les cas chroniques et chez les schizophrènes il n'a procuré aucune amélioration et a parfois accentué les manifestation psychotiques. L'auteur ne tente pas d'interpréter ces données préliminaires, sauf peut être pour déclarer que ces résultats constituent une nouvelle preuve de l'existence de mécanismes organiques à la base des processus psychotiques ou autres manifestation de cet ordre, et aussi que les troubles affectifs et la schizophrénie procèdent de mécanismes différents.

Discussion

DR. JOHN C. SAUNDERS:* It was interesting to hear Dr. Goldman bring out the need for logic in investigative work. We find, in checking the literature on compounds such as Marsilid, that studies in the past apparently were done with very little regard for logic. Otherwise other workers would have arrived at some of the conclusions we have heard expressed. My logic for the use of amine oxidase inhibitors in depressions was based on the fact that both serotonin and norepinephrine levels are reduced in patients in whom depressive syndromes develop while they are receiving phrenotropic drugs; therefore, if one of the enzyme systems that was producing this reduction should be partially inhibited, this syndrome should be alleviated.

It was in February 1955, at the American Psychiatric Association regional meeting in Galveston, Texas, that I suggested to a group of psychiatrists the value of investigating amine oxidase inhibitors, particularly as they relate to psychiatry. I carried on correspondence with a few of these men but it became necessary eventually to join the "do it

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yourself" camp in order to get things moving in this area. We have been working in this field for about fifteen months, and we consider our results preliminary.

Dr. Goldman differentiated between the patients in his private practice and those he treated at a state hospital. We had 2 patients in our original group who were hospitalized, 1 for thirteen years and 1 for nineteen years. It was possible to discharge them after they had received Marsilid therapy. About 17 of this original group are still in the hospital; they are, in fact, still receiving Marsilid therapy. Part of our purpose was to see what long term therapy would do. We noticed that, in the group of chronically ill psychotic patients, it took approximately eight months of therapy before the patients took part in all the activities provided by the hospital, and began to initiate things on their own. Although we did see changes much earlier, they were gradual, and it took a long time for us to be convinced that Marsilid was really moving these people toward recovery. However, in the nonhospitalized patients, we saw very rapid results with Marsilid. Usually about ten or twelve days were required to produce maximum response.

We concluded from our original observations with phrenotropic drugs that they do clear up delusions and hallucinations. However, we stated in the original report from Rockland that Marsilid had little effect on delusions and hallucinations but was administered in order to alleviate depressions. We are actually treating symptoms, and we continue to select our patients on the basis of what has been called "target symptoms" for drug therapy. We then give the drugs to alleviate or modify these symptoms, and our opinions to date on the value of drugs are based on this type of clinical evaluation.

Our studies to date go past the point of mere clinical observation. We are extremely interested in the basic concepts of metabolism, the enzyme systems, and particularly the oxidase enzymes, which seem to be an important key to the understanding of the mechanism of the action of Marsilid. We also hope that these studies will give us more insight as to the etiology of mental diseases.

In conclusion, we agree with the observations made by Dr. Goldman, which confirm our original studies. We hope that others have the opportunity to continue the clinical and biochemical evaluation of Marsilid and similar compounds.

The Administration of Marsilid to Patients with Depressive Reactions and with Various Degrees of Agitation*

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The value of Marsilid‡ (iproniazid) in neuropsychiatric practice for the treatment of mental depression was established by three independent groups at the Regional Research Conference of the American Psychiatric Association in Syracuse, New York, on April 6, 1957. Previous to this, a number of workers had reported on the therapeutic value of Marsilid in various fields of medicine after having noted improvement with administration of the drug. Loomer and associates suggested that it would possibly open a field for the neuropsychiatrist in private practice in treating patients with depressive reactions. This prompted a study that, at the present, is still in progress. Thirty-two patients with depressive reactions and various degrees of agitation were administered this drug, with good results, as an adjunct to the classical organic therapeutic measures for this particular entity. Fourteen other patients with contrasting clinical entities comparable to this condition were individually studied psychiatrically and were examined by an internist of the research staff of Hoffmann-La Roche. The case histories of those selected for this paper follow:

CASE REPORTS

Case 1. The patient was an apathetic, dejected, agitated 67-year-old white man, who gave a history of being depressed for approximately 18 months. This depression was untreated until his case came to the attention of physicians, after he had slashed his wrist and jumped into the ocean. He was immediately hospitalized in a state hospital and received a series of 7 to 10 classical electroshock treatments. He showed some improvement and, against the advice of physicians, he returned home. In a short time he returned in another depressed state, with a gross manifestation of agitation, and was started on a series of Reiter's convulsive therapy. As he was a large man, he was immediately placed upon 50 mg. of Marsilid three times a day.

The results were excellent, and he required only five organic treatments. His wife stated, "After about two weeks on the new medicine he seems to have gradually emerged from the depths in a solid way and he now appears to be himself again." Although he had made excellent improvement and his spirits were evaluated by his family as being within the normal range, as they had always known him, he complained of a certain amount of restlessness and an inability to relax as he felt he should. He was given 5 mg. of prochlorperazine§ three times daily, with very gratifying results. He lost his restlessness, his spirits appeared to be more stable, and he gained 16 pounds of the 26 he had lost in a period of approximately six weeks. His entire physical aspect had changed. He showed no evidence of any psychomotor excitation and his blood pressure was normal. No edema or any other side effect was noted until, about the time of his discharge, he complained of difficult micturition in the morning. He stated that he thought that possibly at his age his prostate had been affected.

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* Read by title.

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‡ Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

§ The trade name of Smith, Kline & French Laboratories for prochlorperazine is Compazine.

His medication was decreased to one-half the amount, and within three days this side effect had disappeared.

This patient was gradually tapered off Marsilid to the point where he was taking only 25 mg./day in divided doses; the drug was then discontinued entirely.

Case 2. This 54-year-old patient was a stockily built, mute, frozen, depressed Negro. His history revealed that five years previous to his psychiatric treatment he had been depressed. The depression progressed until, six months previous to seeking psychiatric help, he just sat; for days he would not get out of bed and spoke to no one, except with guttural noises. Reiter's convulsive therapy was inaugurated, and the patient was administered 250 mg. of Marsilid daily in four divided doses. At the end of six convulsive treatments over a period of 10 days, the patient began to verbalize slightly and to smile. As he appeared to be improving, he was continued on the drug; within three weeks he manifested normal drive and his appetite became normal. He complained of some inability to sleep and was given 500 mg. of ethchlorvynol* at bedtime; his insomnia was relieved. Within a week the patient began to show some evidence of euphoria. When the ethchlorvynol and Marsilid were each reduced to 150 mg. a day, in three doses, the euphoria disappeared and the patient was described by his family as being "himself."

No side effects were noted in this case. There is a possibility that this patient was a psychic manic-depressive in a mild hypomanic phase.

Case 3. The patient was an apathetic, agitated 58-year-old white man who complained of marked "blues," with feelings of loneliness, constant unhappy thoughts that he declined to describe, insomnia, and loss of appetite, which was evidenced by gross malnutrition. He had been admitted to the state hospital on two occasions and discharged with slight improvement. He felt there was no help for him and was contemplating self-destruction at the time he was seen. He was hospitalized in a general hospital and given six Reiter's convulsive treatments; initially, he was administered 75 mg. of Marsilid daily, which was increased to 150 mg. daily after 10 days of hospitalization and on completion of his organic therapy. This patient showed dramatic results, and after discharge from the hospital he continued to improve. He was very receptive to psychotherapy and started to work on his farm and chicken ranch, which he owned but had taken no part in managing during the three and a half years prior to being seen for this program of treatment. He stated that he had never felt better but that he felt a little jittery during the day, and he complained of some insomnia. However, he stated: "It wasn't a bad insomnia, but I just lay there contemplating what I was going to do the next day and formulating my plans for the future." He was given 5 mg. of prochlorperazine three times a day, and 500 mg. of ethchlorvynol at bedtime, which alleviated the insomnia. He expanded his occupational activities and increased his hired help within a month and a half from the time he was first seen. His appetite increased, and he regained 20 of the 40 pounds he had lost. His skin cleared, his color improved, and he evidenced a marked improvement in the peripheral vascular system. All medication was stopped except Marsilid, which was tapered to 75 mg. daily for two weeks. The Marsilid medication was further reduced to 50 and then to 25 mg. every other day for two weeks; finally, all drugs were stopped. No side effects were manifested. The neurologic and physical examinations showed all reflexes physiologic, with no abnormality whatsoever.

Case 4. This patient was a 25-year-old white housewife, with a severe, agitated, depressive reaction. For about seven months previous to being seen she had been depressed, seclusive, wept without cause, and spoke in a grief-stricken manner. Three days previous to being seen she spontaneously demonstrated this agitated phase. She was administered Reiter's convulsive therapy on four successive days and 5 mg. of prochlorperazine three times a day. Three days after the last organic treatment she was given 75 mg. of Marsilid daily in three divided doses, a dose of 2 mg./Kg. of body weight. For approximately six days no agitation was noted; the prochlorperazine was discontinued and Marsilid was increased by 10 mg./day until she was taking 130 mg. daily in three divided doses. Within six days she showed a dramatic elevation of mood and was discharged from the hospital, to be seen on an outpatient basis. Within the next 10 days she began to show a marked in-

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* The trade name of Abbott Laboratories for ethchlorvynol is Placidyl.

terest in her household activities and did the shopping at the local food store. Three months before being seen, she had been extremely frightened of going shopping and had been unable to complete this task. As she continued to improve, Marsilid was cut back to 25 mg. three times daily for three weeks, then gradually reduced within the next two weeks until the drug was discontinued entirely.

Case 5. This patient was a markedly depressed 17-year-old white woman who had made a suicide attempt by jumping into the canal. The patient, an undernourished, disheveled, dehydrated individual with a pronounced acneiform area covering the superior and lateral aspects of both cheeks, ventilated freely at the first interview. She stated that she felt she could not go on in life with the existing acneiform condition, and continued in a process of self-depreciation until she manifested a classical depression. She was started on 25 mg. of Marsilid four times a day and was seen every other day for psychotherapy. Within 10 to 12 days her affect began to improve; she began to discount the suicidal aspects but still requested someone to be with her at all times. Her appetite increased, and as she complained of no insomnia, the dosage was increased to 150 mg. three times a day. She then complained of a mild insomnia, which was alleviated with 500 mg. of ethchlorvynol at bedtime.

The results of the administration of Marsilid were dramatic. Her acneiform condition completely disappeared after a month of medication, and she gained 12 pounds. Marsilid was cut down to 100 mg. daily in divided doses; after 10 days it was reduced to 75, to 50, and then to 25 mg. every other day. This patient showed a remarkable remission and has entered the field of nurses' training. No side effects were displayed throughout the entire period of administration of the medication. Other than ethchlorvynol for insomnia during the period that the dosage of Marsilid was elevated, she received no other treatment except psychotherapy.

SUMMARY

This select group of patients varied widely in age and displayed various aspects of depressive reactions. Other than slight difficulty of micturition, some transient euphoria, and an induced insomnia that was readily corrected, no side effects were noted. The dosage range of Marsilid was quite uniform throughout the program, being held within a range based on the patient's weight, with slightly increased dosages consonant with the depth and display of the depressive reaction.

CONCLUSION

It is evident from the study that the clinical uses of Marsilid for affective disorders in the field of psychiatry show unlimited possibilities; the exploratory phase has only been touched upon. The established fact that Marsilid is compatible with other drugs suggests the possibility that it acts synergistically with some. Studies are now being made to determine its compatibility with other tranquilizing drugs.

RESUME

Ce groupe sélectionné se composait de malades d'âges très variés qui présentaient diverses formes de réactions dépressives. En dehors de légers troubles de la niction, d'une certaine euphorie passagère et d'une insomnie, qui fut rapidement corrigée, aucune réaction secondaire n'a été observée. La marge des doses de Marsilid a été constamment uniforme durant toute l'expérimentation; elle était maintenue dans les limites correspondant au poids

des malades, avec au besoin une légère augmentation de la dose selon l'intensité et les manifestations de la réaction dépressive.

L'étude montre de façon évidente que les applications clinique du Marsilid paraissent devoir être illimitées dans le domaine de la psychiatrie où des troubles affectifs sont concernés. La phase exploratrice n'a été qu'effleurée. Le fait établi de la compatibilité du Marsilid avec d'autres drogues a conduit à envisager la possibilité de l'existence d'une synergie avec certains médicaments. Des études sont en cours pour déterminer sa compatibilité avec certaines drogues "tranquillisantes."

REFERENCE

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Marsilid and Electroconvulsive Shock Therapy

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A year ago the statement "after nearly twenty years of world-wide psychiatric experience, it is now well established that the most consistently reliable treatment for overcoming suicidal melancholia is electroconvulsive therapy," would not have been seriously challenged. Today we know that a considerable number of patients with melancholia need not be given electroconvulsive therapy, but may be treated successfully with the new drug Marsilid.† It is unfortunate that the more radical methods (electroconvulsive and insulin shock therapy) were developed first and that so much time passed before this relatively simple drug treatment came to light.

Unquestionably, certain patients, notably the aggressively suicidal, will still require electroconvulsive therapy. In cases of melancholia (those with the depressed type of manic-depressive breakdown, the well known involutional melancholia, reactive depressions, or psychoneuroses and schizophrenia), it would seem sound practice to give a trial period of therapy with Marsilid, if at all possible, before resorting to the more drastic electroconvulsive therapy. Patients who have already received electroshock therapy may be treated with Marsilid to prevent future depressions and possibly obviate the need for further treatment with electroshock.

In recent years there has been much speculation regarding the effects of various drugs on the mind as well as increasing understanding and knowledge of this important area of medicine. At the September 1957 meeting of the International Congress of Psychiatry in Zurich, Dr. Carl Jung said in part ". . . my approach to the chemical solution of problems presented by cases of schizophrenia is not the same as yours, since I envisage schizophrenia from the psychological point of view. But it was just my psychological approach that had led me to the hypothesis of a chemical factor, without which I would not be able to explain certain pathognomonic details in its symptomatology. . . . I consider the etiology of schizophrenia to be a dual one, namely, up to a certain extent, psychology is indispensable to explain the nature and the causes of the initial emotions, which give rise to metabolic alterations. These emotions seem to be accompanied by chemical processes causing specific temporary or chronic disturbances or destructions."

Electroconvulsive Therapy and Marsilid. Although electroconvulsive therapy has served us well in the past, it seems certain that the large number of psychiatrists who have acquired the complex skills necessary for the proper use of electroshock therapy will welcome the opportunity to supplant it with the simpler chemotherapeutic regimen wherever possible. One need only compare the two methods of treatment to be convinced that Marsilid has many advantages. The more apparent advantages and disadvantages are noted in table I.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

Dosage and Administration of Marsilid. The initial dosage, depending on the individual response of the patient, has been from 25 to 50 mg. of Marsilid three times a day. The maximum dosage used was 150 mg. three times a day. If there is any danger of a manic tendency, the dosage should be cautiously increased, beginning with only 10 mg. of the drug three times a day.

It should be noted that the dosage in each case must be individualized. After the initial trial of 50 mg. three times a day for a week or less (all patients are seen twice a week during the beginning of the treatment period), the dose for the next seven to fourteen days should be redetermined; this should also be done again later in the course of therapy. The psychiatrist must keep careful records of weight, blood pressure, and tendon reflexes, adjusting dosage downward as soon as is indicated by the patient's improvement. This is most important, since serious complications may result if a high dosage of the drug is maintained longer than necessary. For example, for many who require 150 mg. a day to induce remission, the dose can be cut to 75 or 100 mg. a day by the third or fourth week of treatment, and can often be maintained on 40, 30, or even 20 mg. a day after the second or third month of treatment. The criteria for dosage are not yet clearly delineated; thus, careful, frequent observation must be the yardstick.

One reason for the necessity of proper control of dosage levels is the astonishingly rapid weight gain frequently encountered. Reduction of the dosage may assist in control of weight,

TABLE I

Comparison of Marsilid and Electroconvulsive Therapy

Marsilid Therapy	Electroconvulsive Therapy
The patient can continue working; can carry on usual daily routine, for example, drive a car	The patient must take time off from his job for the entire course of therapy; cannot carry on usual routine; is not allowed to drive a car
No social stigma	Social stigma attached
Much easier on the family because of absence of amnesia or confusion, which occurs with electroshock therapy	Generally patients are afraid; requires a long time to persuade them to take it
Can be given to patients with cardiac disease without any danger; edema, occurring in perhaps 5 per cent of the patients, is a temporary metabolic phenomenon	Although methods for giving therapy now safe, these methods have hazards, and considerable time and effort are required to learn technique
If not carefully controlled, can push a patient into a maniacal psychosis	Complications of therapy (fractures) occur in as many as 23 per cent of the patients
Sustained recovery is apparently high when dosage is maintained	Electroshock and insulin shock therapy are uneconomical; results of electroshock are temporary

but the effect of appetite stimulation on persons receiving Marsilid therapy may necessitate dietary precautions, to obviate distortions of the figure.

Another consideration is the possible occurrence of elevation of blood pressure in previously normotensive persons. Blood pressure should be checked frequently while the patient is receiving Marsilid therapy. Reflexes should also be checked before therapy is started as a basis for comparison with later observations. The rapidity of development of hyperreflexia is one of the best measures we have of estimating the altered state of the patient's nervous system.

Ankle edema occurs fairly frequently in persons receiving full doses of the drug; however, it usually recedes in a few days after administration of Marsilid is discontinued and administration of acetazolamide* or chlorothiazide† is employed for a week or ten days. Marsilid can then be safely given in smaller dosages, and edema usually does not recur.

Blood counts should be requested for each patient before treatment is instituted as a basis for comparison with later findings.

Impotence appears to be a frequent yet poorly understood complication of Marsilid therapy and may cause the patient to refuse further medication. It may then become necessary to resort to electroconvulsive therapy, which often brings about a return of potency. Instances of hypererotic activity have been reported.

In patients who represent a suicidal risk, combined electroconvulsive therapy may be indicated during the early phase of Marsilid therapy, since the effect of the drug may not be apparent for the first few weeks of treatment.

It should not be forgotten that chemical and physical therapy cannot eliminate the need for psychotherapy in depressed or schizophrenic patients. The treatment of such patients with Marsilid must, therefore, be supplemented by psychotherapeutic procedures.

CLINICAL RESULTS

The use of Marsilid was not confined to patients on whom a diagnosis of depression was made. Because of the possibility that schizophrenics might be aided by the drug, a number of these patients were treated with Marsilid. Furthermore, depressives other than the manic-depressives and those with involutional melancholia received this chemotherapy. The variety of mental disorders treated with Marsilid is shown in table II.

Some patients have shown such remarkable improvement that it is difficult to assign them a place on an arbitrary scale. But, since the use of an arbitrary scale has merit, the following plan was instituted. A plus was given if there was improvement in any of the categories; no more than four pluses were allotted to any one patient. The following categories were used in evaluating the patients: (1) emotional status; (2) verbalizing capacity; (3) intellection; (4) physical status, i.e., improvement in blood pressure; (5) physical status, i.e., weight gain; and (6) obviation of convulsive therapy. If for any cause the treatment failed, a minus sign was used.

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* The trade name of Lederle Laboratories Division, American Cyanamid Co., for acetazolamide is Diamox.
† The trade name of Merck & Co., Inc. for chlorothiazide is Diuril.

TABLE II

Mental Disorders Treated with Marsilid

Condition	No. of patients
Manic-depressive (depressed)	19
Schizophrenia	11
Reactive depression	9
Involutional melancholia	8
Anxiety neurosis (obsessional neurosis)	7
Alcoholism with depression	3
Depression with senility	2
Inadequate personality	2
Hysteria	1
Neurasthenia	1
Parkinsonism	1
Schizoid personality	1
Total	65

Since it is important to evaluate the need for electroconvulsive therapy, the patients were divided into two groups. The results are summarized in table III.

Of the 12 patients who were assigned minus signs, 10 stopped using Marsilid less than a week after it was first given and thus could not be considered as treated. Two patients were not seen again, so the effects of the drug are unknown.

A total of 50 patients showed various degrees of improvement. Of the 4 patients who were rated only 1 plus improvement, continued treatment may place them in a better

TABLE III

Results in Sixty-Five Patients Treated with Marsilid

	No previous electro-shock therapy	Previous electro-shock therapy	Total
Treatment still being evaluated	1	2	3
No improvement (−)	8	4	12
Slight improvement (+)	1	3	4
Considerable improvement; partial remissions (++)	5	14	19
Markedly improved (+++)	10	4	14
Complete remissions (++++)	10	3	13
Total	35	30	65

status; however, even the present level of 1 plus improvement is a considerable lift over the severe degree of breakdown initially present.

Those with a 2 plus improvement are doing well enough to be considered partial remissions; there are 19 of these patients. The 3 plus and 4 plus patients should, in my opinion, be considered full remissions. The 27 markedly improved, added to the 19 of the 2 plus group, give a total of 46 patients who showed good results of therapy.

Therefore, on the basis of good results in 46 of 50 patients receiving oral Marsilid medication, plus the fact that all of this group have apparently been saved from further electroconvulsive therapy, it must be concluded that this method of treatment constitutes a major breakthrough in the management of malignant mental disease.

CASE REPORTS

Case 1. A 35 year old mother of two children presented a picture of continuous apathy. She gave a heart-rending description of her bedridden state since a hip fracture that had occurred more than a year previously. After prolonged invalidism she was sent to a sanitarium and given electroshock therapy, but upon release from the sanitarium she was far from recovery. Since the apathy had improved but slightly, she was brought to me for further ambulatory electroconvulsive therapy.

She was persuaded with great difficulty to come for intermittent electroconvulsive treatments each month. The patient's husband was convinced that this form of therapy was the only way of making life bearable because of her frequent episodes of mental retardation and sadness.

Administration of Marsilid was then begun, and in less than two weeks her husband reported that he could not believe the improvement that had occurred. The patient now comes to the office neatly dressed, which is in contrast to the untidy attire she had been wearing for two and a half years. Her husband commented, "Those tablets have increased her 'get up and go' like nothing else ever has."

Case 2. A chronic alcoholic, whom I succeeded in "drying out" with psychotherapy and intensive vitamin therapy some eight years previously, returned to me for treatment of anhedonia. Resumption of intensive vitamin therapy with intermittent psychotherapy and a high vitamin, high calorie diet resulted in a gain of only three pounds over a four month period. There was little or no improvement in the chronic depression, the sad voice, and in the phobic overtones. When Marsilid was added to the intensive vitamin regimen, the patient gained 13 pounds in fourteen days, an accomplishment that was impossible, even with insulin therapy, some eight years ago. He is now more animated and talks with no sign of fear or unhappiness in his voice; it seems likely that he can be maintained on this higher emotional plane of eudemonia indefinitely by proper adjustment of Marsilid dosage.

Case 3. A 68 year old woman had received electroshock treatment for severe depression nine years previously. She recovered from that melancholic episode but her condition regressed some months ago. She consulted many physicians without success, and in desperation her husband requested another course of electroconvulsive treatment because of the recurrence of severe depression. He was more than pleased when advised that electroconvulsive treatment might be obviated by the use of a new drug for melancholia.

The patient manifested considerable improvement by the end of the first week of combined Marsilid–pyridoxine therapy. At the end of the second week, she showed an even greater degree of improvement. At that time she described an increase in appetite with improved good spirits. Although she had been unable to help her husband in a mercantile establishment, she now is assuming her full share of these duties. A slight gain in weight has also occurred.

Case 4. Severe alcoholic addiction occurred in 47 year old impotent man who suffered from chronic melan-

cholia. He refused electroconvulsive therapy but has shown the most astounding improvement with Marsilid of any patient thus far observed. Repeated alcoholic episodes occurred, despite promises to remain "dry;" eventually true delirium tremens psychosis developed. This was interrupted by dextrose-insulin and intensive vitamin therapy. The patient then agreed to conditioned reflex therapy with a new drug, calcium carbamonitrile.* While receiving this treatment, with oral and parenteral intensive vitamin therapy, oral choline dihydrochloride, and parenteral testosterone, he showed only fair improvement during a three-week period. The chronic melancholia remained. At this time Marsilid, 150 mg. daily, was instituted. It induced an astonishing feeling of well-being in this man who had obviously been depressed for years. He is now animated and normally talkative when he comes to the office.

Case 5. This patient, formerly a nurse, is the 35 year old wife of another patient, who received electroconvulsive treatment a year ago because of a severe depressive reaction with a mild paranoid coloring.

The wife had held up well during her husband's depression, but depressive tendencies developed when she became pregnant several months after the husband's recovery. At that time her obstetrician did not feel she should have any added medication.

Because her depression showed no signs of recession and because the husband was being constantly bombarded with her melancholy thoughts (including her verbalized compulsion to harm her first-born), the obstetrician conceded that something should be done. When she was brought to me, I urged that chemotherapy be tried before electroconvulsive therapy was even considered. Both the patient and her husband agreed. Within ten days of Marsilid therapy, remarkable improvement was noted with almost complete disappearance of depressive symptoms in two weeks. When last seen, the patient's bright spirits continued and a dosage of 50 mg. of Marsilid a day plus supplementary pyridoxine was maintained. Delivery of a normal girl was uncomplicated.

Case 6. A 43 year old woman came to me in a marked depressive state superimposed on a chronic anxiety neurotic reaction. She had symptoms of severe hypochondria. The chief psychosomatic symptom was a sense of burning in the mouth.

A course of electroconvulsive therapy (12 treatments) given more than a year ago brought about a partial remission of the severe depression but did not improve the somatic complaints, including a burning mouth, intermittent insomnia, stomach butterflies, unbearable tension, fear of being alone, and repetitive excessive fears without apparent objective cause.

Psychotherapy and tranquilizers were given for nearly a year without results. On my urging she took a voluntary job, but repeatedly refused full time employment because she was afraid that her neurotic complaints would make it impossible for her to keep a job.

Despite the fact that it had been assumed that Marsilid might induce exacerbation of anxiety symptoms, it was decided to try drug therapy. Six months' experience with this patient has proved emphatically that Marsilid has made an outstanding contribution in the treatment. The remarkable reduction of previously unbearable tension occurred only during the period of Marsilid therapy. Insight psychotherapy has undoubtedly helped but could not be responsible for this remarkable metamorphosis, which must be credited to drug therapy. She now enjoys a full time paid position.

Case 7. An apathetic, undernourished, young man in his late twenties had great difficulty in deciding on a vocation, despite a college education and army service. Receiving 150 mg. Marsilid daily, he gained 8 pounds in fourteen days and became spontaneously cheerful. With supportive psychotherapy, he changed in four weeks from an indecisive young man to one with strong purpose. He is now receiving a reduced maintenance dosage of Marsilid.

Case 8. A young man, 23 years old, requested help in overcoming a hand tremor and excessive generalized

* The trade name of Lederle Laboratories Division, American Cyanamid Co., for calcium carbamonitrile is Temposil.

tension that had been present since childhood. Before coming to this country three years ago, he had consulted many physicians but had not received help for the tremor. Psychotherapeutic conferences revealed that it distressed him greatly that his hand shook continually while he was standing before his students in the school in which he had taught. He experienced even greater difficulty when he became a restaurant counterman and often feared he would drop dishes.

Since the results of a sugar tolerance test suggested mild hyperinsulinism, frequent high protein meals were advised, resulting in only slight relief. A number of tranquilizers were prescribed, but the tremor and inner tension were not reduced to any appreciable extent.

When Marsilid was given he changed in a short time from a slow-acting, desultory person lacking animation into an optimistic, animated, self assured, and happy young man. He no longer complains of tremor.

COMMENTS

Marsilid in many cases produces a degree of improved well-being that certainly increases tremendously the rapport between the psychiatrist and his patient, making it much easier for the patient to initiate the spontaneous discussions that are required for successful psychotherapy. This is particularly important with introverted (schizoid) persons, who manifest long periods of aphonia that interfere with maintenance of psychotherapeutic contact.

The patient realizes that, in addition to improved well-being and spontaneity induced by chemotherapy, there is constantly available the skill of the psychotherapist, resulting in the enhancement of better rapport between patient and psychiatrist.

It is noteworthy that a patient invariably shows distinct regression whenever an unexpected complication makes it necessary temporarily to discontinue Marsilid. If a moderate degree of well-being has been produced, cessation of drug therapy will result in noticeable mild or moderate depression. This depression may be such that the patient weeps spontaneously and complains of being deprived of the drug.

One of the best uses of this new therapy will be to prevent recurrent depressions. By initiating the administration of Marsilid immediately after any course of electroshock therapy, we believe that additional electroconvulsive therapy may be obviated. Marsilid does not completely eliminate the need for electroshock therapy but it will substantially reduce the number of patients who will require electroconvulsive treatment in the future.

The major advantages of Marsilid in the field of psychiatry include not only the counteraction of melancholia, but also the promotion of optimal conditions for psychotherapy.

SUMMARY AND CONCLUSIONS

Marsilid therapy was begun in a series of 65 patients. Of 50 patients who continued to receive Marsilid, 46 showed either partial or full remission. My limited experience indicates that astonishing improvement can be observed in patients whose conditions previously resisted other methods of treatment. Furthermore, many other patients who heretofore would have been considered candidates for electroshock therapy have recovered from the depressed state without its use.

Unless the patient with melancholia is aggressively suicidal, a four week trial of Marsilid should be given before considering the more radical electroshock therapy. If suicide is

feared, electroshock therapy must be the treatment of choice unless there are extreme physical contraindications.

It is necessary to see the patient frequently during the beginning of Marsilid therapy to determine whether or not depression is receding. Constant supervision by the family or a nurse is indispensable if an increase in the number of suicides is to be avoided. One must remember that there is a latent period of three to four weeks before the full effects of Marsilid are obtained in most patients.

RESUME

Le Dr. Robie a étudié le Marsilid chez des malades atteints de psychose maniaco-dépressive, de mélancolie d'involution, de dépression d'origines diverses ou de schizophrénie.

Parmi 65 malades recevant le Marsilid, 10 ont cessé de le prendre durant la première semaine, 2 ne sont pas revenu chez le médecin, 3 sont encore en cours d'observation. Les 50 autres malades ont tous été améliorés; 46 d'entre eux ont présenté une rémission totale ou partielle. Des malades considérés comme candidats à l'électrochoc sont sortis de leur état de dépression sans y avoir recours. La dose initiale variait entre 10 à 50 mg. trois fois par jour. Le maximum de la dose utilisée a été 150 mg. trois fois par jour. La posologie a été réglée sur une base individuelle selon la réaction du patient.

Il y a lieu de surveiller l'apparition d'effets secondaires, tels que l'augmentation pondérale rapide, l'élévation de la tension artérielle chez des sujets où elle est habituellement basse ou modérée, l'oedème des chevilles, l'impuissance ou l'hyperérotisme et l'exagération des réflexes. La rapidité avec laquelle ce dernier signe se développe est un indice permettant d'apprécier l'altération du système nerveux chez le malade.

Le Dr. Robie pense qu'à moins qu'il ne s'agisse d'un cas avec danger de suicide immédiat, le malade devra recevoir le Marsilid à titre d'essai pendant quatre semaines, pour éviter si possible le traitement par électrochoc. En présence du danger de suicide immédiat, l'électrochoc pourra être indiqué pendant les deux premières semaines de la cure de Marsilid, car il faut parfois deux ou trois semaines pour que l'effet du Marsilid se manifeste.

Marsilid for Elderly Persons

*Edward Settel, M.D.**

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The advent of the tranquilizers three years ago marked the beginning of a new era in the chemotherapy of mental disturbances. Attention has been focused primarily on the positive area, or "hyperactivity," of the emotional spectrum. As a consequence, new drugs for the treatment of the depressed or withdrawn patient were not developed, perhaps because this type of patient presented a less spectacular social problem or did not require the amount of medical and nursing attention as did the destructive, assaultive, overt patient with psychomotor hyperactivity.

However, salvage of the depressed person, whether young or old, is still a matter of vital concern to the profession. Indeed, the high incidence of the depression syndrome in elderly patients is one of the significant problems in current medical and sociological thinking.

Marsilid† (iproniazid), developed several years ago as a drug for tuberculosis, was recently shown to have merits as a psychic energizer in depressed patients.[1, 2] The powerful effect it exerts biochemically in the brain became evident from the work of Brodie, Pletscher, and Shore,[3] of Zeller and his collaborators,[4–6] and of Brodie et al.[7] Briefly, they have indicated that Marsilid, through its inhibitory activity on monoamine oxidase, increases the brain content of 5-hydroxytryptamine and norepinephrine. This biochemical phenomenon manifests itself clinically by a psychic-energizing effect. The latter connotes antidepressant or stimulating action on the affector system. More recent observations by Cesarman[8] have broadened the scope of the possible usefulness of Marsilid to include the treatment of angina pectoris.

This report deals with recent experiences with Marsilid in a group of elderly persons with behavioristic aberrations and personality changes who live in a modern nursing home, where excellent care and detailed observations are possible. In dealing with this type of patient, a simplified psychiatric classification is proposed in order to avoid the controversial and not too clearly defined psychiatric nomenclature and classification of mental diseases.

Between the two clinical extremes of deep depression and complete withdrawal on the one hand, and violent psychotic agitation on the other, there are innumerable shadings, gradations, and combinations. Starting from the negative end of the spectrum, deep withdrawal, there are decreasingly less severe degrees of depression and hypoactive anxiety; these shade gradually into the wide and ill defined central band of so-called normalcy or average. Here, socially acceptable patterns of behavior exist. Further to the positive end of the spectrum there are moderate states of anxiety, tension, and hyperactivity, followed by more intense degrees of agitation, and finally ending in the extreme area of overt manic conduct.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

At the negative end of the spectrum, depression and withdrawal are common findings in the elderly for the following reasons. (1) They have reached the autumn of their lives and their thoughts are occupied, for the most part, with fear of impending death. These feelings, which are a potent factor in the affective life of these patients, whether on a conscious or subconscious level, lead first to concern, then to worry, and finally to abject fear. (2) Those over 65 years of age have often been excluded prematurely from pursuing their occupation in a society that forces them to retire when they may still be able to work at optimal capacity. This, too, may have a seriously depressing effect. (3) The multitude of chronic organic ills that afflict the aged, rendering them invalids either in whole or in part, may make them dependent upon family or society for their sustenance. The very nature of chronic disease, whether cardiovascular, renal, neurologic, or musculoskeletal, adds to the feelings of inadequacy and dependency. Lack of understanding on the part of family and friends creates the perfect milieu for development of depression and withdrawal.

Consideration of an energizing or restorative drug in the field of geriatrics involves the need to point out the hazards inherent in therapeutics for elderly persons. They are known to be highly reactive, even hypersensitive, to drugs of any kind. Therefore, extreme caution must be exercised in the administration of new drugs. When an energizer is used in elderly patients in the treatment of depression, overstimulation must be avoided to prevent a chain reaction that might be set off in other independent organs.

METHODS

Forty-eight depressed patients, whose ages ranged from 64 to 92 years, were treated with Marsilid. Twenty-six women and 22 men were observed for from two to five months.

Initially, the dose of Marsilid was 50 mg. three times a day, given after meals. Subsequent experience necessitated reduction of this dose in many instances. Details and reasons for these changes will be discussed later.

From a psychological viewpoint, all patients exhibited symptomatology at the negative end of the psychic spectrum. They showed moderate to severe degrees of depression and were classified according to their symptomatic psychological diagnoses, as shown in table I. Twenty-seven suffered from severe senile depression, 12 from mild senile depression, 6 from an anxiety depression syndrome, and 3 from a long-standing post-menopausal depression.

TABLE I

Symptomatic Psychological Diagnosis of 48 Patients Treated with Marsilid*

Diagnosis	No. of Patients
Severe senile depression	27
Mild senile depression	12
Anxiety-depression syndrome	6
Postmenopausal depression (long-standing)	3
Total	48

* 64 to 92 years old.

TABLE II

Medical Diagnosis of 48 Patients Treated with Marsilid*

Diagnosis	No. of Patients
Hypertensive cardiovascular disease	30†
Chronic osteoarthritis	9
Simple arteriosclerotic senility	4
Cerebrovascular accidents with sequelae	3
Parkinson's disease	2
Total	48

* 64 to 92 years old.

† 21 patients had advanced myocardial damage, 9 of whom were supported with reserpine derivatives.

The medical diagnoses are listed in table II. Thirty patients had cardiovascular disease, of whom 21 had marked myocardial damage for which full treatment with digitalis and diuretics was required. Many of these 21 patients suffered from intermittent cardiac failure, and their cardiac reserve was poor. Their functional balance was maintained only by salt and water restriction and the other usual supportive measures. The remaining 9 did not require digitalis or diuretics, and were maintained satisfactorily on various reserpine preparations.

Nine additional patients suffered from chronic osteoarthritis, 4 from simple senility with cerebral arteriosclerosis, 3 from the sequelae of cerebrovascular accidents, and 2 from Parkinson's disease.

Preliminary studies of all patients included personality profiles with follow-up interviews to determine the level and context of thinking, as well as mood and manner of interpersonal relationships. Complete physical and neurologic examinations were done weekly. Observations were also made of increase or decrease in appetite and body weight, of sense of well-being, sleeping and eating habits, interest in social environment, and degrees of participation in recreational and occupational therapy.

The nurses in charge were briefed in tabulating certain key points in relation to possible alterations in mood and activity. Special forms were used to record these changes.

TABLE III

*Results of Marsilid on 48 Patients**

Results	No. of Patients	Per cent of Patients
Improved appetite and weight gain	37	77
Mood elevation	40	83
Improved recreational activities	30	62
Better personal hygiene	28	58

* 64 to 92 years old.

Urinalyses, peripheral blood counts, and studies of renal and hepatic functions were carried out initially and at monthly intervals.

RESULTS

Table III indicates the results noted in patients treated with Marsilid. Thirty-seven of the 48 patients (77 per cent) had greatly improved appetites, with subsequent weight gains that ranged from 2 to 16 pounds after less than ten weeks of therapy. Forty patients (83 per cent) showed marked elevations in mood, characterized by better relationships with many phases of the environment. Increased energy was noted, as was a desire to meet and talk with other patients and members of the nursing staff. Thirty patients (62 per cent), who had previously sulked all day or sat motionless in their favorite chairs, came out of their shells to relate themselves to their surroundings and to converse with the staff and with fellow patients. They gradually began to participate in social activities, first by attending parties and games, and later by joining some of them. Twenty-eight patients (58 per cent) became more careful about their personal hygiene and appearance. Some made their own beds, took short walks with attendants, and manifested some interest in club activities and occupational therapy. There were fewer complaints of physical ailments.

Effects on appetite and mood were noticed usually after approximately two weeks of treatment, and became gradually more pronounced, reaching an optimal level during the fifth week. These peak effects were maintained as long as therapy with Marsilid was continued.

The need for extreme caution in administering Marsilid became obvious very soon after institution of the study, when various side effects were observed with the initial dosage schedule of 50 mg. three times a day. Some of these side effects were sufficiently severe to necessitate reduction of dosage to 25 mg. three times daily. If side reactions persisted at the lower dosage, the dosage was further reduced to 12.5 mg. three times a day.

The most serious side reaction was a sharp drop in systolic and diastolic blood pressure. These effects are tabulated in table IV. A sharp drop in blood pressure was noted in 29 patients (60 per cent) receiving a total daily dose of 150 mg. Twenty-two of these patients

TABLE IV

Effects of Marsilid on Blood Pressure

Effects	No. of Patients	Total Percentage of Patients	No. of Patients on Lower Dosage (%)
Sharp drop in blood pressure*	29	60	
Moderate drop in blood pressure†	20	42	69
Minimal drop in blood pressure‡	8	16	40

* 48 patients receiving 50 mg. three times a day.
† 29 patients receiving 25 mg. three times a day.
‡ 20 patients receiving 12.5 mg. three times a day.

were afflicted with chronic hypertensive cardiovascular disease. There was a 30 to 50 mm. drop in systolic and a 10 to 25 mm. drop in diastolic blood pressure. Severe vertigo and staggering accompanied this hypotensive effect, leading to serious falls in several patients. In fact, 1 patient sustained a fractured pelvis and another a fractured patella. There were many instances of lesser trauma. Attempts to counteract this hypotensive effect of Marsilid with ephedrine and neosynephrine given orally produced severe palpitations, headache, and nervousness, and had to be abandoned.

When the total daily dose of 150 mg. of Marsilid was reduced to 25 mg. three times a day for one week in the 29 patients who did not tolerate the higher dose, the blood pressure of 9 patients rose to premedication levels; in 20 the drop was approximately half of that which it had been when the patients were receiving Marsilid at the higher dose level. In the latter, a further reduction to 12.5 mg. three times daily resulted in premedication levels in 12 patients and a systolic pressure drop of only 10 to 20 mm. in 8 patients. This slight decrease of pressure was not accompanied by vertigo and falling.

It is worthy of note that the energizing effect of Marsilid was proportional to the dosage. Thus, on the 12.5 mg. schedule, five to six weeks were required to reach the level of stimulation achieved in two weeks of the 50 mg. dose.

Episodes of congestive heart failure and peripheral edema were more frequently observed in patients with cardiac disease who experienced pronounced lowering of blood pressure. Apparently, in these instances, there was reduced cardiac output with increased water and salt retention. Obviously the elderly patient with advanced myocardial disease is sensitive to rapid diminution in blood pressure, which limits a broader use of Marsilid in such patients, unless they are under close observation and are kept on a conservative dosage schedule.

In 10 patients constipation developed. This was readily ameliorated with mild cathartics. Conversely, there was moderate to severe diarrhea in 7 patients, with some weight loss and demineralization; this was combatted effectively with various types of antidiarrheal preparations and temporary discontinuance of Marsilid. When the drug was reinstituted at a lower dosage, the diarrhea did not recur.

Two octogenarians with borderline azotemia experienced increased nitrogen retention; in 1 patient the blood urea nitrogen rose from 20 to 54 mg. per cent, whereas in the other it rose from 33 to 72 mg. per cent. This increased azotemia fortunately subsided on withdrawal of the drug.

A moderate degree of anemia was observed in 12 patients after 8 to 10 weeks of treatment. In 5 there was a 5 per cent decrease in hemoglobin, in 4 a 10 per cent drop in hemoglobin, and in 3 a 15 per cent drop. Administration of hematinics counteracted this effect.

Mild seborrheic dermatitis developed in 3 patients and this was readily controlled with symptomatic therapy. In 1 patient jaundice developed.

Two patients with anxiety-depression syndromes became increasingly confused and hyperactive on the 50 mg. dosage schedule. On withdrawal of the preparation, these effects subsided and did not recur when the 12.5 mg. dose was instituted.

The patients in this series, who were below 75 years of age, seemed less prone to side effects and tolerated the dosage of 50 mg. three times a day better than did older patients.

Of course, the myocardial and nutritional status of the former subjects was superior to that of patients in their eighties and nineties.

SUMMARY AND CONCLUSIONS

Marsilid was evaluated in a series of 48 elderly patients with moderate to severe degrees of depression and withdrawal. In 62 to 83 per cent of this selected group of patients, the drug produced an excellent energizing effect, characterized by improved mood, increased appetite, weight gain, greater activity, and better relationship with the environment.

Elderly patients are extremely sensitive to drugs, particularly when a significant degree of hypertensive cardiovascular disease is present. The marked hypotensive effect produced in 60 per cent of the patients by a daily dose of 150 mg. of Marsilid frequently resulted in decreased cardiac output with ensuing congestive failure and peripheral edema. These effects were minimized by reducing the dosage, first to 25 mg. and then to 12.5 mg. three times a day. At this dosage level the energizing effect was delayed for from two to three additional weeks, but there was a wider margin of safety.

Other less serious side effects encountered included constipation, diarrhea, anemia, and dermatitis, all readily controllable with symptomatic therapy. Increased confusion and agitation occurred in 2 patients with anxiety-depression. Moreover, the blood urea nitrogen in 2 patients with borderline azotemia increased considerably. The former were able to tolerate the lower dosage level, and in the latter pretreatment levels of blood urea nitrogen were restored by withdrawal of Marsilid.

Marsilid is effective in combatting depression in elderly patients, but it must be used with extreme caution due to the frequency of serious side effects. Most common was a sharp and prolonged hypotensive reaction that could result in congestive failure, pulmonary edema, vertigo, staggering, and falling, which might lead to trauma. Long-standing cases of congestive failure required diuretics and cardiac support in the form of digitalis and oxygen. By reducing the Marsilid dosage to 12.5 mg. three times a day, these reactions were for the most part eliminated, but with the lower dosage the energizing effect developed more slowly.

The physician administering Marsilid to the elderly patient with cardiac disease must be circumspect and must watch his patient with utmost care. If these precautions are heeded, Marsilid will frequently produce improved mood and affective attitudes, and a gain in appetite, weight, and energy without untoward effects.

RESUME

Le Marsilid a déterminé un effet "énergisant" excellent dans un groupe de 48 individus âgés dont le degré de l'état de dépression allait de modéré à sévère. Les effets favorables du Marsilid ont été les suivants: amélioration de l'appétit avec gain pondéral, 37 malades; amélioration de l'humeur, 40 malades; amélioration de l'aptitude à se distraire, 30 malades; amélioration de l'hygiène corporelle, 28 malades.

Le traitement a été poursuivi pendant deux à cinq mois. La dose initiale était de 50 mg. trois fois par jour, elle a été ramenée à 25 mg. trois fois par jour et enfin le patient était

maintenu à la dose de 12,5 mg. trois fois par jour, selon la réponse individuelle à la médication. Les effets secondaires, comme par exemple l'hypotension, qui a été particulièrement observée chez les sujets âgés de plus de 75 ans, ont été minimisés par la réduction de la dose. D'autres effets secondaires, qui furent facilement contrôlés par une thérapeutique symptomatique, comprenaient la constipation, la diarrhée, l'anémie, et diverses réactions cutanées.

Le Dr. Settel déclare en conclusion que le Marsilid est efficace pour combattre la dépression chez le malade âgé, mais en raison de la fréquence de réactions secondaires sérieuses il doit être utilisé avec une extrême prudence. L'auteur ajoute que, compte tenu des précautions à prendre, le Marsilid améliorera l'humeur et les attitudes affectives, l'appétit, le poids et l'énergie sans provoquer de réactions nocives.

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Discussion

Dr. Edward Kent:* It was a pleasure to listen to Dr. Settel's presentation and to learn of the fine work he is doing with Marsilid in the treatment of depressions in elderly patients. Any drug that can produce 62 to 83 per cent improvement in such patients deserves careful consideration.

We began a pilot study with Marsilid in elderly patients at the Brooklyn Hebrew Home and Hospital for the Aged approximately six months ago. The patients at our institution differed somewhat from those studied by Dr. Settel, in that our patients were from a lower socioeconomic level. At least 50 per cent of our cases were in poor physical health and in a precarious emotional status.

As pointed out by Dr. Settel, depressions occur often in the older hospitalized patient. Such trivialities as the inadvertent neglect on the part of the ward personnel to greet a

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TABLE I

Degree of Improvement of 17 Elderly Patients Treated with Marsilid

Mild to Moderate	Good to Excellent	None to Questionable
9 patients (53%)	4 patients (23.4%)	4 patients (23.4%)

patient, to heed a slight complaint at once, or to comply with an unrealistic demand, frequently cause emotional disturbances that might lead to acute depressions.

The patients may become argumentative, obstinate, garrulous, and demanding. Negativism, assaultiveness, disobedience, tearing their clothing, and destroying bedclothes might follow. This is succeeded by poor appetite, insomnia, dejection, helplessness, and hypochondriasis. In extreme cases, the patient is stuporous or agitated. He may refuse to get out of bed or to respond to questions. He may pace back and forth incessantly or may become noisy and yell at the top of his voice, disturbing other patients and ward personnel.

Until recently the only treatment for acute depression was mechanical restraint, drug restraint, or, as a last resort, electroshock treatment. We have also tried such drugs as amphetamine, pentamethylentetrazol, and nicotinic acid, but these have not yielded adequate results and were therefore abandoned.

To date, a total of 17 patients with depressions have been treated with Marsilid at our hospital. Their ages ranged from 68 to 99 years. Of these patients 5 had chronic brain syndromes associated with cerebral arteriosclerosis, 6 had occasioned depressions, 1 had a mixed psychoneurosis, 2 had chronic brain syndromes associated with senile brain disease, 1 had a manic depressive psychosis, and 2 had adjustment reactions of late life.

Initially our patients were given a daily dose of 75 mg. of Marsilid. If this was tolerated well and if it was believed that a higher dose might produce greater improvement, the daily dose was increased to 150 mg. The period of treatment with Marsilid ranged from one to six months. Improvement consisted of better cooperation, appetite, behavior on the ward, and personal hygiene, as well as greater productivity, and less retardation and mood elevation. These changes were observed after one to four weeks of treatment in 13 patients, or in 76.4 per cent. Table I shows the improvement, classified as mild to moderate, in 9 patients (53 per cent) and, as good to excellent, in 4 patients (23.4 per cent). Four patients did not show any improvement.

Five patients died after having received Marsilid for from five weeks to four and one half months. In 3, death was attributed to coronary artery disease; in 1, to generalized arteriosclerosis and diabetes mellitus; and in 1, to bronchopneumonia and generalized arteriosclerosis.

Impressions and Conclusions. Marsilid may become a valuable adjunct in the treatment of depressions in elderly patients. In our study, 76.4 per cent showed improvement of various degrees. This correlates well with Dr. Settel's findings. Five deaths occurred in our group and these could not be attributed to Marsilid. The use of Marsilid deserves further trial and evaluation. I agree with Dr. Settel that special consideration must be given to the side effects that may occur with this drug.

Biochemical and Clinical Changes Resulting from Administration of Marsilid and Tryptophan to Schizophrenic Patients

Biochemical Aspects

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In 1941 my colleague Dr. H. Birkhäuser discovered that the activity of monoamine oxidase in the pallidum of schizophrenic patients deviates from the activity found in the brain of nonschizophrenic control subjects (table I). The difference approximates statistical significance ($P = 0.06$). On the other hand, brain monoamine oxidase can be blocked *in vivo* by Marsilid,† a fact that had been discussed previously and confirmed in several laboratories, specifically in the laboratories of Dr. G. B. Koelle and Dr. S. Udenfriend. We wondered what would happen if Marsilid was given to schizophrenic patients, and what metabolic changes and/or what mental changes would occur after administration of this drug.

It is obvious that in a study of this type the activity of monoamine oxidase should be a limiting factor in the observation. This would hardly be the case if the concentration of the substrates of this enzyme, for example, serotonin and norepinephrine, varied markedly during the experimental period. To secure optimal conditions for our experiment, we took advantage of an observation made in Dr. Udenfriend's laboratory, where it was shown that from 1 to 3 per cent of administered L-tryptophan is converted into 5-hydroxy-L-tryptophan, which in turn is decarboxylated to yield serotonin. We added to the diet 7 μM of Marsilid/Kg./day and 100 μM of L-tryptophan/Kg./day.

Prior to the treatment period a tryptophan load test with 5 Gm. of L-tryptophan/Kg. was carried out with 24 schizophrenic persons and 16 persons without any apparent mental disease. The concentration of xanthurenic acid during the load test reaches higher levels in the urine of schizophrenic patients than in the urine of control subjects (table II). The difference is statistically significant. For another product of the tryptophan metabolism, 5-hydroxyindole acetic acid, the reverse is true. If we consider formation as well as excretion of these compounds as part of over-all tryptophan metabolism, we can conclude that in schizophrenic persons tryptophan metabolism seems to deviate from the norm.

Figure 1 shows the effect of treatment for six weeks on spontaneous daily consumption of protein and spontaneous tryptophan intake, and on ceruloplasmin. The differences are statistically significant.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

TABLE I

*Monoamine Oxidase of Pallidum of Human Brain**

Normal (8 patients)	81 ± 5
Schizophrenics (6 patients)	67 ± 4

* Uptake of O_2 (μl.) during two hours of incubation of 100 mg. of tissue homogenate with 0.01 M tyramine.

TABLE II

*Urinary Excretion of Xanthurenic Acid during the Tryptophan Load Test**

Groups	A	B	C
16 Control subjects	18 ± 6	30 ± 8	41 ± 16
24 Untreated schizophrenics	23 ± 7	43 ± 24	50 ± 46

* Data refer to micrograms of xanthurenic acid per milliliter of urine; urinary fractions in column A were collected immediately before administration of tryptophan, in column B from zero to 2.5 hours after administration of tryptophan, and in column C from 2.5 to 5 hours after administration of tryptophan.

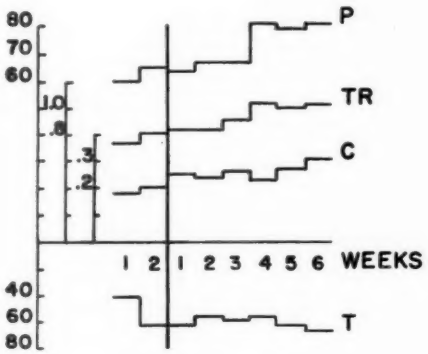

FIG. 1. Daily consumption of protein and of tryptophan, and ceruloplasmin activity; P, protein; TR, tryptophan; C, optical density, measuring ceruloplasmin activity; T, average temperature in Chicago, degree Fahrenheit; vertical line indicates beginning of the experimental period.

Table III shows the decreased excretion of 5-hydroxyindole acetic acid in patients treated with Marsilid and tryptophan. At first the difference was insignificant and then, on the twelfth day, it became significant. At the same time the patients began to change from a psychiatric point of view.

At the end of the six week period of treatment, the excretion of 5-hydroxyindole acetic acid drops by almost half, another proof that the metabolism of serotonin is changed by the

TABLE III

*Daily Excretion of 5-Hydroxyindoleacetic Acid**

Consecutive Days	Treatment Period (days)	5-Hydroxyindoleacetic Acid (mg.)	(P)
1	1†	3.5 ± 0.83	
15	4	3.1 ± 1.48	0.50
23	12	2.4 ± 1.12	0.0
30	19	2.3 ± 1.29	0.06
37	26	2.7 ± 1.69	0.26
44	33	2.5 ± 1.12	0.08
51	40	1.8 ± 1.17	0.01
56	2‡	2.9 ± 1.61	0.46

* The values for hydroxyindoleacetic acid indicate the amount excreted in twenty-four hours as determined in twenty-four hour specimens.

† Pretreatment period.

‡ Post-treatment period.

TABLE IV

*Urinary Excretion of Xanthurenic Acid Before and After Treatment**

Groups	A	B	C
7 Untreated schizophrenics	22 ± 5	24 ± 16	72 ± 61
7 Treated schizophrenics	22 ± 7	30 ± 8	26 ± 9

* See table II.

application of Marsilid. Dr. Voelkel in Germany reported similar results, namely, that the excretion of 5-hydroxyindole acetic acid dropped in subjects treated with Marsilid.

In table IV data on xanthurenic acid excretion during the tryptophan load are summarized. The concentration of xanthurenic acid dropped significantly in the two and a half to five hour fraction after five weeks of treatment of 7 patients with tryptophan and Marsilid. Not only the average but also the range, over which the xanthurenic acid data spread, dropped significantly, as indicated by the so-called F-test.

CONCLUSIONS

We may summarize our experience by saying that there are differences between schizophrenic persons and nonpsychotic control subjects in tryptophan metabolism. The metabolism of these patients seems to be influenced by administration of Marsilid.

RESUME

La conclusion de ce rapport est qu'il existe des différences d'ordre métabolique entre les schizophrènes et les sujets-témoins non psychotiques quant au métabolisme du tryptophan. Chez les schizophrènes, le métabolisme était visiblement influencé par l'administration de Marsilid. Il semble exister une corrélation entre les modifications chimiques et psychologiques qui se produisent simultanément. Le but de l'étude était de mettre en évidence ces relations éventuelles.

Biochemical and Clinical Changes Resulting from Administration of Marsilid* and Tryptophan to Schizophrenic Patients†

The Clinical Aspects

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In this study, the patient population consisted of 7 schizophrenic men between the ages of 26 and 35 years, who had been ill for from two to twelve years. Six of the patients were Caucasian and 1 was a Negro. Four of them were assigned to my service, and I had seen them on daily ward rounds prior to this study. The duration of their time on my service varied from two to nine months. Their physical health was good, and there were no chronic medical illnesses. Each had a rather poor premorbid adjustment, their histories indicating abortive attempts at securing education and employment. Only 1 of the group had married but, although married eighteen months, this patient had not achieved a satisfactory sexual union with his wife. Another patient was working on an M.A. degree when committed. However, he had been hospitalized 6 times for mental illness since 19 years of age, including fourteen months at the Menninger clinic. He had made one attempt at suicide and four vigorous homicidal attacks on his parents during the eleven-year period. One patient had never worked, and 2 had held jobs only for short periods of less than one year. All the patients had undergone previous hospitalization and treatment, including for several of them two or more courses of insulin coma therapy and electroconvulsive therapy and chemotherapy. Three of them had intensive individual psychotherapy of more than nine months' duration, and all had experienced group psychotherapy. Histories indicated that none of the patients had been capable of good interpersonal relationships, even with members of their family.

The milieu in which the patients were studied and had been living prior to the study was an acute intensive treatment center, and they were on either of two closed wards, the larger of the two having a capacity of about 52 beds. In this setting all patients are exposed to daily swimming, softball, basketball, and general gymnasium activities. They spend time daily at occupational therapy or mechanical arts therapy and three times weekly attend recreational therapy, which includes listening to phonograph records, playing musical instruments, and participating in card games. There is a weekly dance with an orchestra, motion pictures are presented two times weekly, and church services are given on Sunday. The staff consists of 12 to 14 experienced nurses, trained attendants, and student nurses.

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* Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

† From the Neuropsychiatric Laboratory and Psychiatric Service, Veterans Administration Hospital, Hines, Illinois.

Also in this setting the patients are given a multiple choice menu two days in advance and they select food from it. If the items they choose do not constitute a balanced meal, the dietician adds the necessary foods to the tray, but their selection is served as ordered. The actual food consumption of our patients was recorded and from this data their protein and tryptophan intake was calculated.

METHODS

During a two week prestudy period, the chemical base lines were determined and each patient was tested with the Minnesota Multiphasic Personality Inventory and evaluated with the Multiscale Rating for Psychiatric Patients. It seemed possible that the experimental period was too short for discernment of psychological changes by classic methods. With this thought in mind, we developed a daily observation chart that consisted of five sections plus comments. Parts I (appearance), III (general mode of behavior), and V (affect) offered a framework of assessing objectively observable behavior that required no interaction between observer and patient. Parts II (quantity and content of speech) and IV (trends of thought) helped to categorize responses of patients to a given interpersonal situation. Two observers worked independently and did not exchange information during the experimental period. The observations were made at various times of the day and under sundry conditions. At the end of the treatment period the two sets of observations were compared to determine what changes occurred and when.

At the end of the fifth week the Minnesota Multiphasic Personality Inventory and the Multiscale Rating for Psychiatric Patients were again administered. The "Cannot Say" category was eliminated from the Minnesota Multiphasic Personality Inventory both times, thereby forcing a choice of "Yes" or "No," which we believed might prove more illuminating, since our patients were so highly ambivalent. By doing this, if changes were to occur, we presumed that they might be more clearly delineated. T scores and standard error of measurement for a score technique were used in evaluation of the data because of the small size of the patient population.

The evaluation of the second Multiscale Rating for Psychiatric Patients was done without reference to the first to avoid prejudicing the results. With this instrument we explored the occurrence of common areas of change which were thought to be similar clinically. The scales were then further analyzed for the group as a whole to determine what changes occurred in the greatest number of patients.

RESULTS

Analysis of the Daily Behavioral Observations revealed that the first changes occurred between ten and eleven days after initiation of combined administration of tryptophan and Marsilid. These changes seemed to occur in four recognizable phases that appeared to be progressive steps of one unfolding process; however, they did not occur in all patients at the same time.

Phase I. The first noticeable difference in behavior among 5 of the patients consisted in a rise of available energy. They seemed restless, and the withdrawn patients began to sit

upright and move about. Three of these patients gave up their customary supine or fetal positions and exhibited a new tonicity of postural adjustment.

Phase II. Increased motor activity compatible with rising anxiety and tension appeared to grow from Phase I. This period occurred during the second to third week of treatment. The patients appeared to have sufficient energy to experience anxiety. They were described as tense and edgy. Their negativism increased and some became argumentative.

Phase III. The awakening of the need for or acceptance of interpersonal relationships appeared at various times in each of the patients, but was observable in most of them during the third and fourth weeks of study. They seemed to seek the support or, at least, the company of various members of the hospital personnel. We noted sibling rivalry and attempts to monopolize our time. Six of the 7 patients had begun to initiate conversations; of these, 2 had not responded well verbally for several months.

Phase IV. This phase occurred in all patients at some time after the third week of treatment and was characterized by an ability to display what is commonly called "appropriate behavior." There was an increase in the expression of feelings that came into the patients' awareness. We do not mean to imply that the patients' feelings were appropriate to the reality situation but their behavior was compatible with their feelings. There was a discernible expression of affect.

Comparisons of the scales of the two Multiscale Rating for Psychiatric Patients revealed on the second one an increase in motor activity, speech, denial of hallucinations, harmony of thoughts and feelings, and eating. A decrease was noted in the areas of cooperativeness and concern with bodily functions. There was not one scale of the 62 used in which all patients showed a change. Six patients exhibited changes on three scales and 5 patients on 11 scales, but these were not of uniform direction or intensity. There was no gross over-all change indicating that the patients were no longer schizophrenic.

One patient was so anxious and aggressive that he could not cooperate for the second Minnesota Multiphasic Personality Inventory. For statistical purposes our group was then reduced to 6 patients for this test. The standard error of measurement for a score technique was the statistical method used to evaluate the data from the Minnesota Multiphasic Personality Inventory. The results of this procedure revealed that, with one exception, all patients manifested some significant shifts between the first and second administration of the test. No changes were accepted unless they fell at the 0.01 or 0.05 level of confidence. Only three scales revealed a shift in behavior by 4 or more patients; these were the Depression, Masculine-Feminine, and Schizophrenic scales. The changes noted on these scales varied from patient to patient and were not of uniform direction or intensity.

SUMMARY

The three tools used to evaluate the results of this study indicate that changes occurred in the patients' behavior during the experimental period. Furthermore, the changes the patients experienced seemed to be primarily at a nonverbal, kinetic, affect level and were not accompanied by any striking alteration in the thinking disorder.

RESUME

Rapport concernant les observations de l'auteur sur 7 schizophrènes du sexe masculin, dont l'histoire révélait l'incapacité d'établir de bonnes relations personnelles, même avec les membres de leur propre famille. Chaque malade recevait une dose quotidienne de 2 mg./kg. de Marsilid (iproniazide). En outre, 20 mg./kg./jour de tryptophan étaient ajoutés au régime alimentaire.

Les changements observés dans le comportement semblent se manifester en quatre phases distinctes, qui paraissent être des étapes progressives du déroulement d'un même processus. Cependant, ces changements ne se sont pas manifestés au même moment chez tous les malades. Durant la phase I (10 à 11 jours), 5 patients ont présenté une élévation du degré de l'énergie dont ils disposaient. Ils commencèrent à s'assoir normalement et à se déplacer. Durant la phase II (2 à 3 semaines), les patients faisaient preuve d'une activité motrice accrue. Ils éprouvaient de l'angoisse et ils étaient nerveux, tendus. Certains étaient querelleurs. Durant la phase III (3 à 4 semaines) le besoin et l'acceptation de relations avec autrui s'éveillaient. Six de ces malades ont eux-mêmes engagé la conversation. Durant la phase IV (après la troisième semaine) tous les malades avaient un comportement "approprié." Ce comportement n'était pas nécessairement approprié à la réalité, mais il était compatible avec les sentiments éprouvés par le malade.

L'auteur signale que les changements observés se manifestaient surtout au niveau affectif élémentaire, non verbal, et ne s'accompagnaient pas d'un changement important dans le domaine de la pensée.

Effect of Marsilid on the Symptoms of Some of the Rheumatic Diseases

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Following the report of Scherbel[1] on the effect of Marsilid† on the various manifestations of rheumatoid arthritis, it was decided to attempt to confirm this work and to observe the effects of this drug on some of the other collagen diseases. This brief report will attempt to summarize some observations made during the past seven months on the effect of Marsilid on 41 patients with rheumatoid arthritis, 1 with rheumatoid arthritis and psoriasis, 7 with rheumatoid spondylitis, 5 with dermatomyositis, 2 with systemic lupus erythematosus, and 1 with undifferentiated collagen disease.

METHODS

Prior to administration of Marsilid, each patient was placed on the usual basic regimen of salicylates, a diet, and physical medicine, as indicated. Minimal doses of corticosteroids or ACTH were used, if required. Marsilid was then added to this basic program. At the beginning of this study, each patient was given an initial dose of 50 mg. of Marsilid three times daily. Experience made it apparent that this dose was too large; consequently the dosage of Marsilid was individualized and varied between 10 and 50 mg. three times daily. No supplementary vitamins were prescribed except on individual indication. The duration of treatment was from two to seven months and averaged 5.3 months. All patients were observed at weekly to monthly intervals. Routine laboratory studies included complete blood counts, sedimentation rates, and urinalyses.

RESULTS

The evaluation of the therapeutic response of these patients to Marsilid has been based on their subjective and objective improvement.

Subjective improvement was first noted in from 5 to twenty days. This manifested itself in an improved sense of well-being. Coincidentally, there was a gradual lessening of pain, improved appetite, and lastly a diminished sense of stiffness.

Objective changes consisted of diminished swelling and redness of the joints, skin, and muscles, improved motion, and less tenderness. Elevated temperatures returned to normal. Muscular strength improved moderately. Weight gain was consistent with improved appetite, but in no case was the weight gain excessive except in the presence of edema. It is notable that during the period of observation, no appreciable change occurred in the size of any subcutaneous nodules or of any rheumatoid cysts.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

There was no significant change in the blood count of any patient, nor were there any changes in the urine. The sedimentation rate returned to normal in one instance. No major improvement was noted in the sedimentation rate of any other patient. In no case was there any worsening of the results of any of these tests during the trial period.

Of the 41 patients suffering with rheumatoid arthritis who were treated with Marsilid both subjective and objective improvement were noted in 18 (44 per cent), subjective improvement alone in 14 (34 per cent), and 9 received no benefit. Thirteen of these 41 patients had required steroid therapy for satisfactory relief of symptoms before receiving Marsilid. After variable periods of treatment with Marsilid, 5 patients required no steroid therapy, and 3 patients were able to reduce their steroid therapy by 50 per cent.

One patient suffering with rheumatoid arthritis and psoriasis was treated with Marsilid and salicylates. Marked subjective and objective improvement of the arthritic manifestations was noted. The skin lesions improved at a somewhat slower rate than the joint symptoms, but they had almost entirely disappeared within six weeks.

The 7 patients with rheumatoid spondylitis obtained the most remarkable degree of improvement noted in any group of patients in this study. Every patient exhibited marked subjective and objective improvement. Two patients without paravertebral ligamentous calcification became completely asymptomatic. Two patients with incomplete cervical ligamentous calcification had an increase of 50 per cent mobility of this area. Two patients with moderate calcification of the dorsal ligaments had an increase in chest expansion of one inch. Two of the patients with spondylitis required steroids for adequate symptomatic relief before Marsilid was instituted. Subsequent to this therapy, 1 patient was able to discontinue the steroid, and the condition of the second was well controlled with 50 per cent of the previous dose of steroid.

Marsilid was used in the management of 2 patients with systemic lupus erythematosus and 1 patient with undifferentiated collagen disease. Each of these patients showed definite subjective and objective improvement. The elevated temperature returned to normal in each instance, and 2 of the 3 women improved sufficiently to perform most of their housework. Both of these patients were able to discontinue the use of steroids. The third patient was ambulatory and able to care for herself, but unable to work. The steroid requirements were reduced by 75 per cent.

Marsilid was administered to 5 patients with dermatomyositis. One of these patients became asymptomatic (subjectively and objectively), but the atrophic musculature failed to regenerate. Significant subjective improvement was obtained in 3 patients, although there was no definite evidence of objective improvement. One patient became worse. Two of these patients with dermatomyositis had been receiving steroids before administration of Marsilid was started. One of these was able to discontinue the hormone, and the second was well maintained on 50 per cent of the pre-Marsilid requirement.

UNDESIRABLE REACTIONS

Undesirable effects of Marsilid have occurred quite frequently and have varied in im-

portance. Some of these effects have been mild and have had a tendency to diminish, even with continued administration of Marsilid. Others, somewhat more severe, have been adequately controlled by reducing the dose of the drug. Only a few of these side effects have been so severe as to require discontinuation of the drug. In no instance have any of the undesirable effects failed to clear up completely subsequent to the withdrawal of Marsilid.

Minimal to moderate dryness of the mouth occurred in almost every patient receiving Marsilid. Only 13 patients complained about this symptom, and in no instance was it necessary to reduce the dose or discontinue use of the drug. Mild constipation was of such frequent occurrence that it was not recorded and required no treatment beyond increasing the intake of water. In 17 patients constipation required the use of mineral oil but did not require a significant reduction in drug dosage. Difficulty in voiding urine occurred in 3 patients, this responded promptly to a 50 per cent reduction in the dosage of the drug. Two men had decreased libido. In one instance this responded to a reduction in the dose of Marsilid, whereas in the other the drug had to be withdrawn.

Facial and ankle edema was noted in 8 patients, 3 of whom required withdrawal of the drug for relief. The others improved with maintenance of a smaller dosage level. This facial and ankle edema was particularly severe and intractable when it occurred in patients who were receiving corticosteroids with Marsilid. Muscle spasms, twitching, tremors, and involuntary movements were present in 7 patients, and in each instance were preceded by insomnia. Fortunately, these symptoms always improved after the dose of Marsilid was suitably lowered. Light-headedness, vertigo, and orthostatic hypotension proved to be the most severe complications of Marsilid therapy. These symptoms occurred in 11 patients, and in 4 they were of sufficient severity to require bed rest for from five to seven days and discontinuation of the drug. The other 7 patients were able to continue taking a smaller amount of the drug.

The hypotensive action of Marsilid was of benefit to 7 patients who were hypertensive. Six of these patients were normotensive while taking Marsilid, and the seventh had a marked reduction in the systolic and diastolic pressures. Another instance in which an undesirable reaction of Marsilid was beneficial was seen in 2 patients who were suffering with ulcerative colitis in association with a rheumatic disease. In both patients bowel function became normal, possibly as a result of the constipating effect of the drug.

SUMMARY

During the period of this study, a significant percentage of the patients observed had a definite amount of either objective and/or subjective improvement of rheumatic complaints. The laboratory evidence of improvement was conspicuous by its absence. Undesirable actions of the drug were present in a relatively large number of instances. Some of these side effects could be ignored, a smaller number were eliminated or made tolerable by reduction of the dose of Marsilid. In a few patients with severe hypotension, marked edema, or persistent muscle spasms, it was necessary to withdraw the drug. Two of the undesirable

actions, namely, hypotension and constipation, were used to advantage in the management of hypertension and ulcerative colitis.

Since the collagen diseases may have periods of spontaneous remissions, the duration of this study (seven months) was too short to arrive at any definite opinion as to the ultimate value of Marsilid in their management. It is believed that an extensive clinical evaluation of Marsilid should be carried out, using the double blind method, in many clinics and evaluating the results by Lansbury's criteria.[2] It would also be advisable to study the effects of Marsilid on the tissues of such patients by obtaining multiple biopsy specimens, as well as by determining any changes in the various related metabolic processes.

RESUME

Le Marsilid (iproniazide) a été administré à 41 patients atteints de polyarthrite chronique évolutive et à 16 patients atteints de collagénoses diverses. Les stéroïdes ont été également administrés à doses minimes quand cela a été nécessaire. La durée du traitement était en moyenne de 5,3 mois.

Une amélioration subjective, y compris la sensation de bien-être, la réduction graduelle de la douleur, l'augmentation de l'appétit et l'atténuation de la sensation de rigidité, a été observée dans les cinq à vingt jours. Les modifications objectives consistaient en diminution du gonflement et de la rougeur des articulations, de la peau et des muscles; amélioration de la mobilité; diminution de la sensibilité des tissus; accroissement modéré de la force musculaire; abaissement de la température quand elle était élevée; augmentation pondérale en rapport avec l'augmentation de l'appétit. L'auteur n'a pas constaté de changement appréciable des dimensions des nodules ou des kystes rhumatoïdes. Les examens de laboratoire n'ont révélé aucune modification significative de la numération globulaire ou de l'urine.

Bien que des effets secondaires aient été fréquemment rencontrés certains se sont atténués en dépit de la prolongation de la cure. D'autres réactions furent contrôlées de façon adéquate par la réduction des doses. Dans tous les cas, les effets secondaires indésirables ont disparu après interruption du traitement.

Quoique l'hypotension et la constipation soient considérées comme des effets secondaires du Marsilid, ces réactions se sont montrées favorables chez 8 des malades de l'étude. Le Marsilid a fait baisser la tension artérielles chez deux hypertendus et un autre malade atteint de colite ulcéreuse a bénéficié de la constipation provoquée par le Marsilid.

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The Effect of Marsilid in Patients Having Rheumatoid Arthritis

The Theoretical Causal Role of Certain Amine Oxidases

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It is well known that a variety of clinical features occurring in patients with rheumatoid arthritis are related to the central nervous system, but their significance and relationship to objective joint manifestations are not clear. An explanation for their presence in patients with rheumatoid arthritis and their possible relationship to mesenchymal inflammation and fibroblastic proliferation is proposed.

Manifestations Related to the Central Nervous System. The majority of patients in whom rheumatoid arthritis develops complain of chronic exhaustion or easy fatigability for months or even years before the onset of objective joint manifestations. Often an emotional shock or a physical strain appears to initiate the objective musculoskeletal features of the disease. As the disease progresses, fatigability, emotional instability, depression, insomnia, and anorexia may occur singly or in various combinations. Excessive perspiration, involving the head, neck and upper chest, and palms and soles, may occur, and is increased by slight exertion or emotional tension. Pallor, flushing, intolerance to cold, hyperesthesia, paresthesia, and other types of vasomotor reactions may occur. Muscular atrophy may develop rapidly in the presence of minor joint manifestations, suggesting that disuse is not the cause in all instances. Hyperreflexia may occur at the onset of joint manifestations; later in the disease it may disappear or hyporeflexia may appear.

CLINICAL EFFECTS

In June 1952, we began to study the effect of Marsilid† administered to patients having rheumatoid arthritis or related diseases.[1] Alterations in central nervous system manifestations occurred consistently. The first changes to appear were elevation in mood, increased relaxation, and disappearance of anorexia and insomnia. After a few weeks or months excessive sweating and vasomotor activity subsided. Improvement in muscle tone and strength followed, accompanied by increased activity of deep tendon reflexes. Decreased libido appeared in the majority of patients, constipation in approximately one-third, and postural hypotension only rarely when the dosage of Marsilid was 50 mg. daily or less. Early in our investigation it became apparent that Marsilid had a cumulative effect and that only 50 mg. daily was needed initially to produce a desirable effect in patients having rheumatoid arthritis, after which time the dosage could be reduced depending upon the individual needs.

Marsilid, in the usual dosage of 50 mg. daily or less, which usually has been found sufficient to alter central nervous system manifestations, had no significant effect on inflammatory joint manifestations or on fibroblastic proliferation. However, in 3 patients in whom toxicity from

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

overdosage developed early in our investigation, inflammatory joint manifestations diminished temporarily only to reappear as toxicity subsided. In an attempt to determine whether or not Marsilid in higher tissue concentrations would suppress mesenchymal inflammation, 100 mg. of Marsilid solution was injected into actively inflamed joints. This resulted in no significant suppression of mesenchymal inflammation.

Overdosage. Early in our investigation 5 patients with active rheumatoid arthritis were receiving 150 mg. of Marsilid daily. Between the second and third months of treatment, generalized hyperactivity appeared suddenly, manifested by marked hyperreflexia, generalized clonus, excitement, and insomnia. Two of the patients had persistent clonus that lasted for three days after medication was stopped. During this time hepatic function was temporarily altered, retention of sulfobromophthalein sodium ranging from 20 to 29 per cent. Serum bilirubin remained normal. Cholinesterase levels (pseudocholinesterase) were greatly reduced for five to seven days in 4 of the 5 patients. Results of cephalin flocculation and thymol turbidity tests were difficult to interpret due to pre-existing plasma protein alterations.

THEORY ON MECHANISM OF ACTION

Recently serotonin has been considered to enter into the functions of the autonomic and central nervous systems. The amine is believed necessary for normal mental processes, and interference with its action in the brain leads to mental disorders and neurologic dysfunction.[2] It has been suggested that serotonin rather than acetylcholine may be the neurohormonal agent for the central parasympathetic system and that norepinephrine may be the chemical transmitter of the central sympathetic nervous system.[3] Since it is known that Marsilid inhibits the activity of amine oxidases, which in turn inactivate certain amines, including serotonin, epinephrine, norepinephrine, and histamine, it is assumed that improvement in central nervous system manifestations in rheumatoid arthritis is related to release of neurohormones that ordinarily would be inactivated by amine oxidase. It has been reported that excretion of norepinephrine is decreased in patients with rheumatoid arthritis, resulting in an altered excretion ratio of norepinephrine to epinephrine, and that an infusion of 0.1 per cent procaine hydrochloride, a potent inhibitor of monoamine oxidase, causes an increase in the secretion of norepinephrine, resulting in a normal ratio of norepinephrine to epinephrine.[4]

Observation in our patients suggests that the central and peripheral autonomic nervous systems, as well as cholinergic somatic nerves to muscle, are affected by amine oxidase inhibition. If it is assumed that a neurohormonal defect exists, it would appear that these changes are a result thereof, but it does not necessarily mean that serotonin is the defective neurohormone. Perhaps acetylcholine is the defective neurohormone whereas serotonin, when it is present in amounts greater than normal, is capable of assuming the role of a chemical transmitter of nerve impulses in cholinergic nerve fibers. Increased muscle tone and later muscle spasm, together with increased tendon reflexes following the administration of Marsilid, suggest that there is decreased activity of acetylcholine or serotonin before treatment and that delayed inactivation of serotonin will improve the neurologic dysfunction. The frequent association of constipation and decreased libido, with the increased incidence of postural hypotension, suggests that in these patients a compensated state rather than a

true reversal of the neurologic abnormality occurs as far as improvement in the central nervous system manifestations is concerned.

THEORETICAL RELATIONSHIP OF CENTRAL NERVOUS SYSTEM MANIFESTATIONS TO THE MESENCHYMAL REACTION

Mesenchymal inflammation and fibroblastic proliferation, characteristic of rheumatoid arthritis, vary greatly and never have been adequately explained. Because of the central nervous system alterations in rheumatoid arthritis that appear to be related to one or more of the amines inactivated by the amine oxidases, we have begun to study the effect of these amines on mesenchymal tissue. Two of the amines, serotonin and histamine, when administered in minute quantities, were found to be tissue irritants capable of producing an acute synovial reaction. The intraarticular administration of 10 gammas of either serotonin or histamine into an interphalangeal joint in a normal person will cause erythema and swelling. The reaction may not appear for two to three minutes and usually disappears after 20 to 30 minutes (fig. 1). In patients with active rheumatoid arthritis, intra-articular injection of the same amines in the same dosage resulted in an exaggerated reaction that began within seconds and lasted up to eight hours (fig. 2). In addition, dusky cyanosis appeared in all the fingers, except the one that was injected, and at times involved the entire hand following the injection of serotonin. The injected finger was erythematous and moderately swollen. The finger injected with histamine usually was more swollen; however, diffuse cyanosis was

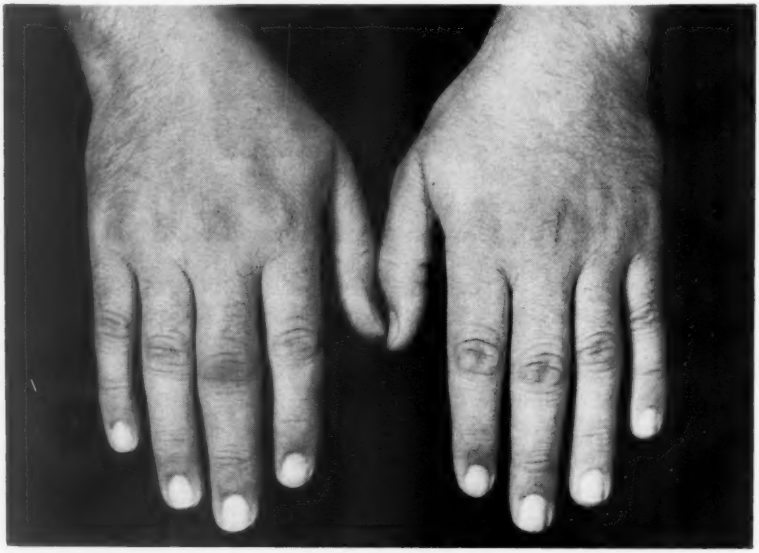

FIG. 1. Normal joints twenty minutes after injections (histamine injected into proximal interphalangeal joint, middle finger, right hand; serotonin injected into same joint, left hand.

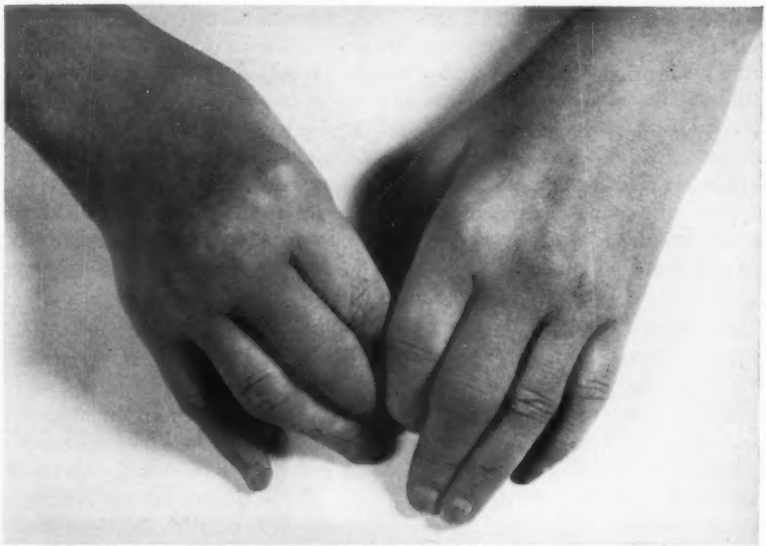

FIG. 2. Patient with rheumatoid arthritis twenty minutes after injections into joints previously normal in size (histamine injected into proximal interphalangeal joint, middle finger, right hand; serotonin injected into same joint, left hand.

not produced. As disease activity subsides, following therapy with anti-inflammatory agents, the reaction produced by those amines diminishes and eventually resembles that produced in normal persons. From these observations it is believed that both amines, when present in a free state in mesenchymal tissue, are capable of initiating an acute reaction: the spread of the amines through the tissues is rapid when disease activity is present but slow when it is absent, and the inactivation of the amines occurs more rapidly in the normal state. The diffuse cyanosis seen following the injection of serotonin in patients having active rheumatoid arthritis indicates that vasoconstriction occurs, probably reflexively. These findings suggest that in the active disease state there is increased tissue permeability and the amines are not destroyed quickly and efficiently.

The relationship between serotonin and proliferation of fibrous tissue is only theoretical at present, and further investigation will be necessary before significance can be attached to the numerous descriptions of fibrotic right-sided valvular heart lesions and fibrous tissue masses surrounding pelvic organs and lower abdominal arteries in patients with carcinoid tumors.

SUMMARY

I have presented our working concept of certain biochemical alterations in patients with rheumatoid arthritis. It would appear that diminished neurohormonal activity accounts

for central nervous system manifestations. This diminished activity could be the result of decreased synthesis or excessive destruction by increased amine oxidase activity. The characteristic inflammatory and proliferative lesions in tissues outside the central nervous system may be related to an overabundance of certain amines that are capable of producing inflammatory reactions and stimulating fibroblasts. Theoretically, this biochemical abnormality could result from increased synthesis of these amines or decreased activity of the amine oxidases in the peripheral tissues.

For some reason, as yet inexplicable, it would seem that patients with rheumatoid arthritis have decreased amine action in the central nervous system and increased amine action in the peripheral tissues.

RESUME

L'effet clinique de l'iproniazide (Marsilid) chez les malades atteints de polyarthrite chronique évolutive a été étudié pendant cinq années. C'est au niveau du système nerveux central que les changements observés à la suite de cette médication ont été les plus constants. Les premiers résultats observés consistaient en amélioration de l'humeur, en relaxation plus marquée et en disparition de l'insomnie et de l'anorexie. Au bout de quelques semaines ou de quelques mois, l'excès de sudation et d'activité vaso-motrice s'atténuait. Le tonus et la force musculaire augmentaient en même temps que l'activité des réflexes tendineux profonds.

Les effets secondaires comprenaient une diminution de la libido, la constipation dans un tiers des cas et, rarement, l'hypotension posturale lorsque la dose n'était que de 50 mg. ou moins par jour.

La dose usuelle était 50 à 75 mg. par jour, ou moins, selon les besoins du malade. A cette dose, on a observé que le Marsilid n'exerçait pas d'effet appréciable sur les manifestations articulaires inflammatoires, ni sur la prolifération fibroblastique. Avec une dose quotidienne de 150 mg., il se produisait des réactions secondaires telles que l'hyperactivité, l'exagération des réflexes, le clonus généralisé, l'excitation et l'insomnie. Au cours de cette période, la fonction hépatique était temporairement altérée et la concentration de la cholinestérase était considérablement réduite.

L'auteur remarque que dans la polyarthrite chronique évolutive, les changements qui se produisent au niveau du système nerveux central semblent en relation avec une surabondance de certaines amines telles que la sérotonine ou l'histamine. Il suggère que chez les sujets atteints de la forme active de l'affection la perméabilité des tissus est augmentée et les amines ne sont pas assez rapidement et assez efficacement détruites.

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The Role of Marsilid in Patients with Far Advanced Cancer

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The care of the patient with far advanced cancer includes three main aspects, namely, (1) control or palliation of the tumor, (2) control of pain, and (3) supportive care. Control or palliation of cancer can be achieved by surgical, roentgen ray, and/or chemotherapeutic procedures, and by hormone therapy. It is not the object of this paper to comment on such therapy. It is sufficient to say that the patients in this report were largely maintained on chemotherapy with phosphoramides.

Pain can be controlled by a variety of narcotic agents. However, control of chronic or prolonged intermittent pain without resultant patient deterioration from narcotics requires skillful management. Any agent that reduces this problem is appreciated.

Supportive therapy is part of the total care of patients with tumors. Cancer is a chronic disease that produces the least psychological, economic, and physical distress when the patient remains self sufficient. In our clinics, small maintenance doses of adrenocorticotropic hormone and/or cortisone have in the past proved the most helpful of all adjunctive agents tried. In order to have some measure of comparison of achievement with Marsilid,† only patients who had been receiving steroid therapy were studied. Cortisone was discontinued and Marsilid substituted.

Table I lists the types of tumors in this group of patients. There were 5 men and 17 women; their ages ranged from 23 to 78 years, an average of 51 years. Eleven were living at the time this article was written; 11 had died. It should be emphasized that all these patients had extensive disease, which had recurred after repeated surgery, and roentgen ray and hormone therapy.

The dosage ranged from 50 to 100 mg. daily in divided doses. The duration of therapy was 3 to 162 days, an average of 55 days. To date, 7 patients are still receiving Marsilid therapy.

Table II lists the desirable effects obtained from Marsilid in this group of patients. Elevation of mood was observed in 10 of these patients. Three patients who were continually depressed and jittery whether receiving cortisone therapy or not were markedly improved by administration of Marsilid. One of these patients cheerfully drove her car and managed her household, in spite of widespread osseous metastases and severe anemia secondary to the disease. The others exhibited varying degrees of gratifying improvement in spirits. Weight gain over that achieved by adjuvant cortisone therapy was noted in 4 patients. Two patients noted improvement in appetite and another noted disappearance of distressing

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

morning nausea. It was noted that 2 patients required less of the mild narcotics used in our clinics.

The side effects from Marsilid therapy are listed in table III.

TABLE I

Adjunctive Therapy with Marsilid in Patients with Far Advanced Cancer

No. of Patients	Type of Tumor
8	Mammary cancer
1	Cancer of the large bowel
1	Cancer of the pancreas
3	Cancer of the ovary
3	Cancer of the uterus
2	Testicular tumors
1	Leiomyosarcoma
1	Neurogenic cancer
1	Lymphosarcoma
1	Primary tumor unknown

TABLE II

Results of Adjunctive Therapy with Marsilid in 22 Patients with Far Advanced Cancer

No. of Patients	Desirable Effects
10	Mood elevation*
4	Weight gain (3 to 8 pounds)
2	Decrease in pain; less narcotic required
2	Improved appetite
1	Disappearance of morning nausea

* In 3 patients with nervous depression, marked improvement occurred.

TABLE III

Side Effects of Marsilid Therapy in Patients with Cancer

No. of Patients	Side Effects	Comments
1	Psychosis	Manifest after thirty days
1	Dizziness	Disappeared after reduction of dose
3	Rash	Aggravation a mild abnormality in 2 patients
1	Nausea	Began after two days of therapy, then occurred with each dose
1	Vomiting	Began in three days; possibly related to cough
1	Pyrosis	Transient early in therapy
2	Decrease in appetite	Related to cortisone withdrawal?
2	Stiffness of joints	Related to cortisone withdrawal?
1	Weakness and hypotension	Related to cortisone withdrawal?

RESUME

Le Marsilid a été administré comme médication de soutien à 22 malades atteints de cancer avancé. La dose s'échelonnait entre 25 et 50 mg. deux fois par jour. Avant le traitement par le Marsilid, des stéroïdes avaient été administrés dans le même but à chacun des malades. En cas de besoin, on administrait aux malades des phosphoramides à doses d'entretien pour contrôler la tumeur et des narcotiques pour calmer la douleur. La durée de la cure de Marsilid a été de 3 à 162 jours.

Les résultats révèlent que le Marsilid a procuré des effets satisfaisants dans 19 cas sur 22, *10 malades* ont présenté une amélioration de l'humeur, *4 malades* ont augmenté de poids, (1,360 à 3,600 kg.), *2 malades* ont pu réduire leur dose de narcotique en raison de la diminution des algies et *1 malade* a observé la disparition d'une nausée matinale.

Certains effets secondaires ont été observés:

Une psychose se manifesta au bout de trente jours de traitement chez 1 malade; des vertiges se produisirent chez 1 malade (la réduction des doses les ont fait disparaître), un érythème apparut chez 3 malades, des nausées survinrent au bout de deux jours de traitement et se reproduisirent successivement avec chaque dose, chez 1 malade le pyrosis fut temporaire au cours du traitement, et chez 1 malade il y eut des vomissements, probablement en rapport avec la toux. L'auteur a également observé la diminution de l'appétit chez 2 malades, la raideur articulaire chez 2 malades, l'asthénie et l'hypotension chez 1 malade. Ces deux derniers effets secondaires, selon l'avis du Dr. Bateman, peuvent être imputables à la suspension des stéroïdes.

A New Approach to the Treatment of Acne Vulgaris

A Preliminary Report

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Since the cause of acne vulgaris is unknown, therapy has been symptomatic. Attempts to treat theoretical causative factors have failed in many cases. Few patients have improved following therapy involving elimination diets, hormones, and vitamins. On the whole, it appears that superficial roentgen ray therapy, or ultraviolet light, and locally applied remedies such as sulfur or resorcinol are moderately effective as control measures. Since it has been observed that rigid adherence to an elimination diet and a strict schedule of washing or scrubbing the affected areas caused rebellion, feelings of guilt, and inevitable discouragement, these methods were dropped four years ago, and a perceptible increase in improvement resulted in most patients. In July 1955, a chance observation led to what may prove to be a promising gain in the treatment of acne.

A 32-year-old woman presented severe, scarring, cystic acne on the face. She had had two complete courses of superficial roentgen ray therapy between 1953 and 1955, as well as large doses of vitamin A and injections of toxoid, and she had adhered to a strict elimination diet, as well as a regimen of frequent scrubbing of the face. Masking make-up had been forbidden. Since her position as an executive in a large department store seemed in jeopardy, she was emotionally upset and had broken off all social contacts. Examination revealed very few comedones; the skin of the face was red and raw. Although the diagnosis seemed obvious, the possibility of rosacea-like tuberculid was also entertained, but permission to take a biopsy specimen was refused. The emotional state of the patient demanded immediate consideration and chlorpromazine, 25 mg. three times daily, was prescribed. Because of the remote likelihood that the condition might be Lewandowski's disease, 100 mg. of Marsilid† three times daily were also given. Use of pancake make-up was encouraged, and the restrictive diet and frequent washing of the affected areas were suspended.

The patient was asked to return after two weeks, instead of after the customary one week interval, as another means of relaxing an onerous regimen of therapy. On the second visit, marked improvement was obvious, not only in the eruption but in the patient's emotional status. After two months the face was wholly free of eruption, with much less scarring than anticipated. Medication was gradually reduced over the next two months, and then discontinued. There has been no recurrence.

Certain questions immediately come to mind. Had the diagnosis of acne vulgaris been correct? Which drug, if any, was responsible for the excellent result? Was a combination

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† Marsilid is the trade name of Hoffmann-LaRoche, Inc. for iproniazid.

of both drugs necessary? How much of the result was attributable to a fortuitous patient-doctor rapport, relaxation of a compulsion-inducing regimen of therapy, and other psychological considerations? During the following twenty months an attempt was made to answer some of these problems.

Since it was planned to treat a group of patients over an extended period, available reports on the pharmacology and toxicity of the hydrazides were studied.[1] Although reports were conflicting, 150 mg. daily appeared to be an adequate dose. Side effects were minimal at this dosage for both isoniazid and Marsilid.

METHODS

Patients with acne vulgaris were divided into three groups without regard to age, sex, race, or severity of the lesions. Those in group 1 received 50 mg. of Marsilid three times a day; those in group 2 received the same dose of Marsilid plus a tranquilizer, and those in group 3 were treated with a tranquilizer alone.* Short, suberythema doses of ultraviolet light were administered to almost all patients on each visit. No roentgen ray therapy was used.

All patients were observed for at least two months, and some for as long as one year. Because most of the patients were seen only every two or three weeks, increments of improvement, when present, were more readily noted. Blood counts were done at random in 34 patients, and no significant abnormalities were observed.[1] Complaints attributable to Marsilid were restlessness, insomnia, and increased constipation. Three men experienced loss of libido; only in these patients was the drug discontinued. In the group receiving ataraxics, there were 2 patients in whom jaundice developed and 3 in whom urticaria developed; these reactions may have been due to sensitivity to the drugs used.

RESULTS

Improvement, manifested by clearing of the eruption, became apparent in an average of three to four weeks. Comedones still were present in about half the patients. Best results were seen in those in whom the condition was more severe. Patients in their twenties and thirties improved more rapidly than did adolescents. Most striking was the surprisingly slight scarring that followed severe, deep acne. This might have been more apparent than real, and might have been due to tissue edema. However, this hypothesis proved unlikely, for in some patients the expected deep pits failed to appear a year or more after cessation of treatment.

Table I lists the results obtained. It is obvious that the best results were obtained when Marsilid was used alone. The addition of a tranquilizer in many cases produced undesirable side effects, but it was observed that hyperkinetic persons, as well as those who experienced

* The tranquilizers used were promazine or chlorpromazine in doses of 25 mg. three times a day. The trade name of Wyeth Laboratories for promazine hydrochloride is Sparine. The trade name of Smith, Kline & French Laboratories for chlorpromazine hydrochloride is Thorazine.

TABLE I

Treatment of 130 Patients with Acne Vulgaris

No. of Patients	Excellent Results	Good Results	No Improvement to Slight Improvement	Medication
50	20 (40%)	24 (48%)	6 (12%)	Marsilid*
47	18 (39%)	21 (44%)	8 (17%)	Marsilid* and tranquilizer
33	2 (6%)	10 (30%)	21 (63%)	Tranquilizer alone

* Dosage, 50 mg. three times a day.

"jitters" as a result of the Marsilid, were benefited by the addition of a tranquilizer. The poorest results were obtained with the tranquilizers alone.

COMMENTS

It is natural to inquire why Marsilid should be helpful in the treatment of acne vulgaris. Although this report does not purport to speculate on the cause of the condition, the author believes that emotional factors may play some part in the cause, or at least in the aggravation, of the disease. Scherbel[2] has reported on the value of Marsilid in depressed patients with rheumatoid arthritis, and it is possible that the effect in persons with acne has a psychogenic basis.[2, 3] On the other hand, Marsilid is known to protect serotonin, epinephrine, and norepinephrine through its action on monoamine oxidase, so that its effect on acne may be by some such mechanism.[4, 5]

Because of the fear of possible toxicity of a relatively unknown drug, only minimal and apparently safe dosages were employed. It is conceivable, however, that an increase in dosage may be warranted in some cases, since no major toxicity was observed.

SUMMARY

A group of 130 patients with acne vulgaris was divided into three subgroups and studied. The groups treated with Marsilid alone, with Marsilid and a tranquilizer, and with a tranquilizer alone.

Marsilid was found of adjunctive value in the treatment of acne vulgaris. Further study of the effectiveness of this drug in the treatment of acne and related skin conditions appears warranted.

RESUME

Une étude d'une durée de vingt mois a été effectuée pour déterminer, dans le traitement de l'acné, la valeur du Marsilid associé aux tranquillisants, ou celle de l'un ou l'autre de ces composés administrés séparément.

Cent trente patients atteints d'acné ont été observés à intervalle de deux à trois semaines pendant au moins 2 mois. Cinquante malades recevaient uniquement le Marsilid, 47 malades recevaient le Marsilid plus un tranquillisant et 33 malades recevaient uniquement le tranquil-

lisant. Les tranquillisants utilisés étaient la promazine et la chlorpromazine. En outre, des rayons ultra-violets étaient appliqués à doses subérythémateuses à chaque visite et à presque tous les malades—la radiothérapie n'a pas été utilisée.

Bien que les meilleurs résultats aient succédés à l'administration du Marsilid seul, l'adjonction d'un tranquillisant s'est montré favorable chez les sujets agités, ainsi que dans les cas ou le Marsilid provoquait l'excitation. L'amélioration, qui se manifestait par le blanchiment de l'éruption, est devenue apparente dans une moyenne de trois à quatre semaines. Des comédons étaient encore apparents chez environ la moitié des malades. Ce sont les cas les plus graves qui ont le mieux répondu au traitement et l'affection s'est améliorée plus vite chez les jeunes adultes que chez les adolescents.

Les inconvénients imputables au Marsilid comprenaient l'agitation, la constipation et l'insomnie. Trois hommes ont éprouvé une déficience de la libido; ce n'est que chez ces malades que le traitement a été discontinué. Trente pour cent des malades recevant le Marsilid ont accusé une amélioration de leur état général. Lorsque les tranquillisants ont été utilisés, l'ictère s'est produit chez 2 patients et l'urticaire chez 3. Dans le groupe recevant uniquement un tranquillisant, les malades se sont fréquemment plaint de somnolence ou de sensation d'étrangeté; ces réactions étaient moins fréquentes chez ceux recevant à la fois le Marsilid et un tranquillisant. Aucun cas d'addiction n'a été observé pour l'une quelconque des drogues utilisées.

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Discussion

Dr. Conrad Stritzler:* I noted with interest that Dr. Bleiberg found Marsilid of value in treating persons with acne vulgaris. I regret to say that this is not in accordance with our own experience.

When I was invited to discuss Dr. Bleiberg's paper, trials with Marsilid were initiated in 20 patients with this cutaneous disorders whose ages ranged from 13 to 18 years. They all received an initial daily dose of 50 mg. of Marsilid three times a day. In addition, a tinted

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lotion containing sulfur and resorcinol was used topically, since it has been difficult to obtain the cooperation of patients with acne unless topical remedies were prescribed. A great deal of difficulty was encountered in maintaining some of these patients on 150 mg. of Marsilid daily, since dizziness, irritability, muscular twitching, and insomnia occurred. Most patients were much more comfortable on a reduced dosage of 50 to 75 mg. daily. Ten patients similarly afflicted were given a placebo and the same topical medication.

Following one month of therapy, 4 of the patients taking Marsilid, or 20 per cent, and 3 patients of the control group, or 30 per cent, showed considerable improvement. Thus there was no significant difference in the response of the two groups. It is true that several of the patients were better adjusted to the acne while they were receiving Marsilid than when they were not. They said they thought they were better, but objectively there was little difference in improvement between the two groups of patients. I realize that the number of patients studied is small, and that the subjects were observed for only a short period, so that these findings can only be considered preliminary. However, we plan to continue our studies with larger groups.

I confess I am unable to find any rationale for the use of Marsilid in persons with acne, since there is no evidence that amino oxidase, epinephrine, norepinephrine, or serotonin plays any role in this disorder. Nor is there any satisfactory evidence that emotional influences play a primary role in the pathogenesis of this condition, although a secondary emotional influence is undeniable.

Although the cause of acne is not clearly established, it is well known that loss of testicular function results in clearing of acne, and surely one must agree that a great deal of emotional trauma is associated with such an event.

The essential pathogenesis of acne involves the development of keratin plugs deep in the neck of the sebaceous glands, which have been conditioned by some unknown factor most apt to occur during adolescence. This unknown factor operates only in the presence of androgens of testicular, ovarian, and/or adrenal origin. Marsilid does not appear to have any known effect on keratin metabolism or on androgens.

The effects of antibiotics in acne have been well documented. It would be difficult to conceive of antibiotics regularly influencing a disease that has an important emotional component.

I should like to add that we have had an opportunity to study the effect of Marsilid on 43 patients with psoriasis, 16 with discoid lupus erythematosus, 3 with sarcoidosis, and 8 with nummular eczema.

The results in patients with psoriasis and discoid lupus erythematosus were unquestionably poor. Doses of 50 mg. three times a day caused a high incidence of dizziness, hypotension, difficulty in urination, constipation, twitching, and insomnia. In 1 man and 1 woman urinary retention developed and catheterization had to be done. In most patients it was necessary to reduce the dose to 25 mg. three times a day. All patients were observed for from one to three months. Acute guttate psoriasis in 1 patient cleared within a week. After receiving 25 mg. of Marsilid three times a day for two months, acute urinary retention suddenly developed. This patient is 1 of the 2 previously mentioned in whom catheterization

had to be done. The remaining 42 patients with psoriasis showed questionable improvement or no improvement after one to three months of therapy.

In 6 patients with discoid lupus erythematosus, who had been maintained on chloroquine, the condition flared up when Marsilid was substituted. One patient with early discoid lupus erythematosus improved rapidly. The other 9 patients with lupus erythematosus failed to show any improvement after one to three months of treatment.

All 3 patients with sarcoidosis were able to tolerate a daily dose of 150 mg. of Marsilid without any complaints. Two of the patients improved considerably after one month of therapy, and the third began to improve after three months of treatment. Improvement occurred both in the cutaneous and pulmonary lesions. Since, in some patients with sarcoidosis, improvement occurs spontaneously, we are as yet not prepared to say that Marsilid influences this disease. However, results have been interesting, and we intend to try Marsilid on as many patients with sarcoidosis as we can.

Finally, we treated 8 patients with nummular eczema for approximately one month with 150 mg. of Marsilid daily and unguentum aqua rosae topically, and no improvement occurred. Three patients in a control group have been followed for only two weeks (as of November 19, 1957), and they show no improvement.

In conclusion, therefore, I am unable to see any role for Marsilid in persons with diseases of the skin other than tuberculoderma and possibly sarcoidosis.

Effect of Marsilid on Weight and Growth of Children*

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The observation that Marsilid† phosphate exerts a favorable influence upon appetite and weight gain was made by clinicians during their early studies of isonicotinic acid hydrazide and its derivatives, first in patients with severe pulmonary tuberculosis, and more recently in patients who were treated with these compounds for rheumatoid arthritis and mental illness.

Let us review briefly the highlights of the experience of other workers concerning the effects of Marsilid upon appetite and weight gain. Robitzek and his colleagues,[1] who in 1952 studied isoniazid and iproniazid in patients afflicted with severe pulmonary tuberculosis, stated, "Anorexia, in the group under study, was encountered with monotonous regularity. Following institution of therapy there was usually a rapid improvement in appetite. This, too, appeared to vary with the dosage. Weight gain was observed at a dose level of 2 mg./Kg./day. Above the 4 mg. level of Marsilid, resumption of appetite was invariable. Appetites became ravenous. . . . On the wards utilized in this study, third, fourth and even fifth helpings have been the rule. . . . Some patients have exhibited gains of 3 to 5 lbs. every week."

Similarly, Bloch et al.[2] reported that 29 subjects, or 85 per cent, of the 34 patients with pulmonary tuberculosis treated with Marsilid exhibited an average weight gain of 9 Kg. Bloch and his associates made a strong point of the fact that the symptomatic effects of Marsilid, such as a striking increase of appetite, weight, and sense of well-being and a decrease of pulmonary symptoms, exceed by far those of isoniazid and other antimicrobial agents or their combinations now in use for the treatment of tuberculosis.

Scherbel[3] reported that a gain in weight was the most consistent objective response in 26 of the 30 patients with rheumatoid arthritis whom he treated with Marsilid.

Smith,[4] who described the beneficial effects of Marsilid in patients with mental illness, stated that of the 10 patients who took the drug at a dose level of 2 mg./Kg./day for two weeks or longer, 9 gained from 6 to 8 pounds and that 6 felt their appetite improved after the seventh day of treatment. Cardis[5] claimed that Marsilid has an anabolic effect, the mechanism of which, he commented, had not been determined.

From the foregoing and from similar reports one could hope that Marsilid might be the answer to the perennial problem of most mothers from every economic strata of every nationality who have children who will not eat. Usually the doctor is requested to give

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

such a child some tonic that would alter his poor eating habits and make him grow heavier and taller. The study to be presented was undertaken to determine whether or not Marsilid stimulates appetites and increases the weight and height of children who fall into this category of "poor eaters."

CASE MATERIAL AND PROCEDURE

The study was conducted at a municipal shelter for underprivileged children who came from broken homes, who were essentially well, and who, as a group, were smaller and less well nourished than a comparable group of average children in the community.

The medication was given as syrup containing 25 mg. of Marsilid per 5 cc. in the form of Marsilid phosphate. For control purposes a placebo syrup was used, matching the active medication in taste, color, and consistency. Both materials were administered in a double blind fashion. So far 40 children have been included in our trials.

All subjects were under constant expert observation so that reliable records on appetite and changes in weight and height could be obtained. Weight and height responses were determined at weekly intervals. All necessary precautions were taken to be certain that the medications were administered as prescribed and that the same type of food was offered to all children, who were permitted to eat as much as they desired. (Extra helpings of bread, meat, and milk were available at all times.)

The 40 subjects, whose ages ranged from 6 to 13 years, may be conveniently divided into three groups. The first group consisted of 10 boys (age range 6 to 9 years) who received Marsilid at a dose level of 2 mg./Kg./day for nine weeks and subsequently were given placebo medication for the same period. The second group consisted of 10 girls of the same age range who were first placed on the inert syrup for nine weeks, followed by a daily dose of 2 mg. of Marsilid/Kg. for the same period. Thus the subjects in these two groups served as their own controls. Of the 20 children constituting the third group, whose ages ranged from 6 to 13 years, 9 subjects received Marsilid at a dose level of 3 mg./Kg./day for two to twelve weeks and 11 subjects were given placebo medication for similar periods. In this group the children were not divided according to sex. Most of them have not yet completed the twelve-week course of medication contemplated, and they have not been used as their own controls.

RESULTS

In the first group of ten boys, some of the subjects showed considerable increase in weight while they were receiving Marsilid, but the weight gains were equally remarkable during the period in which they were receiving the placebo medication. Conversely, the weight of the other children failed to increase while they were receiving Marsilid, but they gained during the period of placebo medication.

In the second group of 10 girls, considerable weight increases occurred during the phase of placebo medication. In general, the increments during the following period of Marsilid administration were smaller, or the gains during placebo medication were not maintained during the subsequent period of Marsilid administration.

The height increments during the period of Marsilid medication of these boys and girls

TABLE I

Weight and Height Responses of Children to Marsilid and a Placebo

Medication	Average Weight (pounds) Initial	Final	Average Gain (pounds)
Boys			
Marsilid	53.94 ± 2.4	55.50 ± 1.97	1.64
Placebo	56.89 ± 2.0	58.79 ± 2.0	1.90
Girls			
Placebo	48.67 ± 1.57	51.75 ± 1.32	3.08
Marsilid	52.30 ± 2.0	52.68 ± 2.00	.38

Medication	Average Height (inches) Initial	Final	Average Gain (inches)
Boys			
Marsilid	48.19 ± .78	48.94 ± .78	0.75
Placebo	49.80 ± .73	50.03 ± .73	0.13
Girls			
Placebo	49.50 ± 1.8	50.03 ± 1.7	0.53
Marsilid	50.24 ± 1.9	50.96 ± 1.8	0.75

indicated considerable growth response. In some instances height increments were comparable when these subjects received placebo medication.

Table I shows the average gains in weight and height of the 10 boys and 10 girls in the first two groups studied while they were receiving Marsilid and the placebo medication. It appears that the average weight increases during the placebo phases were greater in both groups than during the Marsilid phases; in fact the girls gained eight times as much during the period of placebo medication as they did during the period of Marsilid administration.

In contrast, the average gains in height were greater in both groups during the Marsilid phases than during the periods when the placebo medication was given. However, these differences are not statistically significant.

No striking increase in appetite was noted in the children of both groups while they were receiving Marsilid. The boys did not show a diminution of appetite when placebo medication was substituted for Marsilid.

In 1 girl vertigo developed one week after initiation of Marsilid. She was placed in the infirmary and signs of an upper respiratory infection developed within twenty-four hours. After three days the patient made a complete recovery. When Marsilid was reinstituted, vertigo did not recur. Consequently the previous episode of dizziness cannot be attributed to the medication.

The weight and height gains to date of the children included in the third group who were receiving 3 mg./Kg./day during the period of Marsilid medication have not shown striking differences from those receiving the placebo medication.

COMMENTS AND CONCLUSIONS

It is realized that our sample is a limited one in that it includes only subjects between 6 and 13 years of age. It is possible, but not likely, that the weight response to Marsilid of children under or above this age may be more marked than that observed in this study. We deliberately did not include younger children until we were convinced that Marsilid does not elicit untoward effects in younger patients. Furthermore, it is recognized that the Marsilid dosage used in the first two groups, as well as in those receiving treatment for nine weeks, may be inadequate to produce more significant results. With this in mind, the daily dose of Marsilid was increased and the period of its administration prolonged in the third group of children.

Finally, one may conjecture that the weight gains exhibited by the 10 boys in the first group receiving the placebo medication may be a late response to the preceding administration of Marsilid for a nine-week period. This, however, is improbable since the weight gains of the 10 girls included in the second group who initially received placebo medication were considerably greater during that period than the weight gains of the 10 boys during the placebo phase that followed the period of Marsilid administration.

Whether or not Marsilid given at a dose level of 3 mg./Kg./day for a twelve-week period would produce more marked results remains to be seen, but the initial findings suggest that the effects will not be more significant than those observed when children who are permitted to eat as much as they desire receive placebo medication. A dose of Marsilid of 4 mg./Kg./day, which produced the dramatic weight increases in adult patients with severe tuberculosis as reported by Robitzek et al.,[1] has not been tried in children, and the effects of this dosage level should also be studied.

From our findings it would appear that the increases in appetite and weight that occurred in patients with tuberculosis, arthritis, and mental disease at dosage levels of Marsilid used in our study are probably related to a reduction in toxicity of the disease processes and to psychic stimulation rather than to a direct anabolic effect.

In conclusion, then, our study indicates that Marsilid, given at a dosage level of 2 mg./Kg./day for nine weeks does not produce a significant increase in appetite, weight, or height in undersized but otherwise normal children 6 to 9 years of age.

RESUME

Ces études indiquent que le Marsilid n'a entrainé ni l'augmentation subjective de l'appétit, ni l'augmentation du poids et de la taille dans un groupe d'enfants normaux, mais insuffisamment développés, lorsqu'il a été administré à doses de 2 à 3 mg./kg. jour pendant 8 à 9 semaines.

Il semble que l'augmentation de l'appétit et du poids observée avec ces doses chez les malades atteints de tuberculose, de maladies rhumatismales ou de troubles mentaux, dépend vraisemblablement plus de la réduction de la toxicité du processus pathologique et d'une stimulation du psychisme, plutôt que d'un effet anabolique direct. On ne sait pas encore si l'emploi de doses plus élevées, par exemple, 4 mg./Kg./jour, procurerait des effets aussi spectaculaires que ceux observés chez des malades tuberculeux.

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Discussion

Dr. C. William Daeschner, Jr.:* I think Dr. Luhby and his associates are to be congratulated on the careful way in which this study was conducted. Our studies are, unfortunately, less extensive, but they have been carried out in a similar manner. Because of the earlier reports of rapid weight gain in from one to two weeks, we chose to use three week periods, and initiation of any sort of therapy was preceded by a three week period of observation during which no medication was given.

During this period of observation, weight gain was poor. During the period in which Marsilid or the placebo was given, the weight gain was uniformly better than during the initial period. Nevertheless, in this smaller group of patients, our results were similar to those obtained by Dr. Luhby and his associates in that we could distinguish no essential difference in weight gain between those children given a placebo and those who were treated with Marsilid.

It should be emphasized that weight gain and growth in children are not linear functions of time. There are periods of fast and slow growth. It is in these periods of normally slow growth, particularly between the ages of 2 and 6, that parents become disturbed over the nutritional status of their child. This often leads to rather severe conflicts between the parents and the child. This natural conflict between mother and child—the mother expressing her desire to see her child do well, and the child simply experiencing a physiologic anorexia—may become so severe, as Dr. Luhby has mentioned, that it creates a real psychogenic anorexia, which may persist long beyond the normal period of physiologic anorexia. It would seem that, in situations like this, suboptimal nutrition may actually occur. Therefore, in selecting our patients, we chose only those children whose mothers complained of poor appetite or poor weight gain in their children. No other physical complaints were noted. In spite of this selection, no significant difference was noted.

A word about the dosage is always in order when we treat children, particularly small children. Since we plan shortly to extend our observations to infants, we used a dose of 80 mg./square meter, which, in the age group studied by Dr. Luhby, is similar to the dose of 3 mg./Kg. used by him. But since metabolism, renal function, caloric intake, and blood concentrations

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are better related to surface area than to body weight in children less than 8 to 9 years of age, we believed that we would undertreat children of 1 to 2 years if we used 3 mg./Kg., and that we might produce excessive symptoms if we used larger doses in the older children. Therefore, we selected a dose of 80 mg./square meter as equivalent to an adequate adult dose, that is, a dose of approximately 50 mg./day.

Finally, it is worth while to consider what is accomplished when medication is administered to produce weight gain. Have we produced an intake of calories in excess of metabolic needs, with weight gain manifesting only an increase in the deposition of depot fat, or have we actually increased the sensitivity of certain body organs, such as muscles, bones, and connective tissues, through the normal effects of the growth hormone, with an increase in lean body mass as well as depot fat?

With this problem in mind, we have begun using an indirect method of assessing relative body weight—that of measurement of skin folds. To date, increments in body weight in children have been too small to reveal anything. Although these are indirect and certainly not ideal methods of assessing lean body mass, at least they offer some indication of what type of gain is being achieved.

We watched for such side effects as euphoria, insomnia, irritability, anxiety or hyperactivity, weakness or hypotension, hypertension, and constipation, and saw no such reactions in the patients treated with Marsilid.

Treatment of Autistic Schizophrenic Children with Marsilid

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Child psychiatrists are confronted by two situations in which drug therapy would be expected to be helpful. The first is the treatment of hyperkinetic children of varying etiology. In this regard, one thinks first of the organic child, characterized by being hyperactive, destructive, distractable, and impulsive. There is also the schizophrenic child, who may present hyperactivity accompanied by anxiety, body image difficulties, and problems of identification and relationships. In neurotic behavior disorders, hyperactivity may be one of the major presenting symptoms, along with anxiety and defenses against anxiety. For this general group, the tranquilizing drugs developed over recent years have been of inestimable value.

Quite different from the above group are the children who are characterized by being withdrawn, remote, retarded, and in poor contact or out of contact with their environment. I am referring to children who have been diagnosed as schizophrenic children of the autistic type. When one sees such children, one often thinks there should be some way, some drug that will stimulate such a child and make him more alert, aware, and active. Until recently, we have had no success in our search for such a drug. The amphetamines, when tried, have been quite unsatisfactory in this particular group of children. They have had either no effect at all or have made the child worse by producing a state of extreme agitation.

The author and his colleagues, at the close of a study with a number of tranquilizing drugs in children, stated the following: "Actually, the goal in drug therapy in children is not solely one of attaining agents which will subdue and pacify destructive and agitated children. Another problem is the procurement of drugs that will stimulate the withdrawn and autistic child, help the integration of the poorly coordinated child, and stimulate the development of the immature child."[1]

It was therefore of particular interest to learn of the psychiatric use of Marsilid.† Here was a drug that was described as a "psychic energizer," of value in the treatment of mild and severe depressions. It was stated to have a stimulating effect on mind and mood. A trial of Marsilid in autistic, withdrawn children was embarked upon soon after reading these reports.

Fourteen children treated with Marsilid are reported at this time. All these children have been diagnosed as having childhood schizophrenia of the autistic type. The criteria of diagnosis have already been described in the literature.[2]

Several of the children fell in the category described by Kanner[3] as early infantile autism.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

These are children who, from birth or in the first 2 years of life, give clear evidence of extreme remoteness and unrelatedness. Prominent among other symptoms is the necessity of sameness. Current opinion is to classify these children as a subgroup of childhood schizophrenia.[4]

In other children in the experimental group treated with Marsilid, the first two or three years of life had been characterized as essentially normal, although, retrospectively, one could see evidence of precursors of the subsequent psychopathy. However, all of the children, for considerable periods prior to drug therapy and at the time of the drug therapy, presented behavior that could be characterized as autistic. Living in worlds of their own, they displayed a particular disability to relate themselves to other children or adults; in some this unrelatedness also extended to objects. There was evidence of language difficulties, such as mutism, echolalia, deficient speech, and language of noncommunicative value. Their general level of activity was retarded.

MATERIALS AND METHODS

Our series consisted of 10 boys and 4 girls. The age range of the boys was from 4 to 10 years; that of the girls was from 4 to 6 years. The sex distribution, of course, is characteristic of childhood schizophrenia, in which there is marked preponderance of boys over girls. Sex ratios of two to one and four to one are described by various authors.[5]

This group of patients was drawn from three places: 6 of the patients were seen at a day care center for schizophrenic children in Brooklyn, 3 were seen in a hospital setting, and the remaining 4 were seen in private practice.

It should be emphasized that this study was embarked upon purely as a scouting expedition. If some indication would appear that Marsilid were of value in the treatment of these very difficult children, it would be worth while studying the effects of the drug more intensively in controlled study conditions. Therefore, major reliance was placed on clinical observation. No attempt was made to administer placebos at that time. Sources of information were personal observations during clinical examination and reports of parents, colleagues, the staff at the day center, and others.

Observations of the children were divided into 11 categories, as indicated in table I. Under pathologic symptoms were grouped such items as hallucinations, introjected bodies, and bizarre preoccupation with space and time. Observations were made of problems in relationships with other children and with adults.

I might mention that we had some difficulty in organizing the marking of language, since we had 3 children who had some language ability. On the other hand, most of the other children were mute, so we attempted the use of a "double standard." If the child was completely mute at the beginning of therapy, he was classified as 2 minus. Then, if he started some babbling, he would be rated as 1 minus, and if he showed great drive and marked babbling, he was rated as zero. This actually is a tremendous change for these severely disturbed children.

On the other hand, if a child had some use of language, at least a few words, before treat-

ment, we would also classify his condition as 1 minus. Thus, a baseline of evaluation for each child was determined prior to the beginning of drug treatment. Then, while the child was on Marsilid, he was scored for his manifest behavior each time he was observed.

Two of the children reported had been on Marsilid two months; the others had been on the drug for from four to six months. The children were begun on a dose of 0.5 mg./pound for two weeks and were then raised to 1 mg./pound for the next four to eight weeks. If there was no clinical response and sleeplessness was not a major problem, the dose was raised to 2 mg./pound. Only 2 children of this group were on this higher dosage; at the present, we have not treated any children with a dose higher than 2 mg./pound.

Medication was given in elixir form as it was more acceptable to the children than any pill.

At the time of assembling these data, the composite observations in each category were evaluated for change on a five point scale, as indicated in table II. A score of 2 plus indicated a definitely marked improvement; 1 plus, moderate improvement; zero, no or slight change; 1 minus, moderate aggravation of the condition; and 2 minus, marked aggravation.

RESULTS

The results of this study are summarized in table III. The numbers at the top indicate each of the categories that are indicated in table I. The extent of improvement or aggravation for each child in each category is indicated by the plus, zero, or minus scores. Thus, for example, the first child (M-1) showed marked increase in awareness of other children, adults, and objects. There was moderate increase in motor activity, language usage, and time of reaction. The only other change observed was in affect—the child became more cheerful. In other categories, no change was observed.

In order to assign a number to the changes observed in each case, the plus scores were added up and the minus scores subtracted; the total is indicated in the last column. It can be seen that in 2 cases, namely, cases 3 and 14, no improvement was observed; as a matter of fact, in three categories the child became worse. Aside from these 2 cases, there was some improvement noted in every case.

TABLE I

Categories for Evaluation

1. Awareness of other children
2. Awareness of adults
3. Awareness of objects
4. Motor activity
5. Language
6. Reaction time
7. Manifest anxiety
8. Pathologic symptoms
9. Affect
10. Relationship problems with other children
11. Relationship problems with adults

TABLE II

Scoring for Evaluation

− −	Unawareness of people and objects; marked hypoactivity; muteness (no attempt to speak or babble); very slow reaction to command or stimuli or unresponsive; marked depression; marked anxiety approaching panic; severe relationship problems with children and adults.
−	Moderately decreased awareness of people and objects; moderate hypoactivity; language present, but retarded for age, or some drive for babbling; moderately impaired responsiveness; moderate degree of anxiety depression; relationship problems with adults and children.
0	Usual awareness; motor activity, reactivity, anxiety and problems of relationship anticipated for this chronological age; normal affect; language normal for age or marked pressure for speaking.
+	More alertness for surroundings than usual; moderate hyperactivity; language better than expected for age; increased reactivity; moderate degree of elation and moderately better relationship with other children and adults.
++	Keenly aware of surroundings; excessive hyperactivity; very superior language facility; markedly increased reactivity; marked freedom from anxiety; euphoria; remarkable freedom from problems with other children and adults.

TABLE III

Results

	Categories for evaluation											
Child	1	2	3	4	5	6	7	8	9	10	11	Score
1	++	++	++	+	+	+	0	0	+	0	0	10
2	+	+	+	+	+	0	0	0	0	0	0	5
3	0	0	0	0	0	−	−	0	0	0	−	−3
4	0	+	+	−	0	0	+	0	0	−	0	1
5	+	++	+	+	+	+	0	0	0	0	+	8
6	++	++	+	+	++	+	0	0	+	+	0	11
7	0	+	0	+	++	+	0	0	0	−	0	4
8	0	++	0	+	++	+	0	0	+	−	0	6
9	0	+	0	++	+	+	0	0	0	− −	0	3
10	++	++	+	+	++	+	0	0	+	0	0	10
11	+	++	0	+	+	+	0	0	0	0	+	7
12	++	++	+	+	++	++	0	0	+	+	0	12
13	+	+	0	+	+	0	0	0	0	− −	−	1
14	0	0	0	0	0	−	−	0	0	0	−	−3

In certain instances, such as in cases 4 and 13, the areas of improvement were just about balanced out by areas in which there was aggravation. Thus, in 4 cases, there was scarcely any significant change; in 3 (2, 7, and 9), although there was improvement, it was not marked, and was of a random nature. The remaining 7 patients showed change over a wide variety of items. The improvement appeared unrelated to sex: 2 girls showed definite improvement and 2 showed failure to improve.

Age did not appear to be an important factor: of 7 children above the age of 7, 3 showed distinct improvement, and of the 7 below the age of 7, 4 showed distinct improvement.

Again, if one breaks down the data as to time of onset—at birth or subsequently—8 of the children appeared to be ill from birth or the first six months of life. Of these 8, 4 showed distinct improvement. Of the 6 whose illness seemed to have occurred some time after birth, 3 showed distinct improvement.

Most children who did show some change usually improved after two weeks of therapy or at least after four weeks. Of those children who showed no significant change, 2 received the drug for a period of somewhat over one month, but 2 had been treated for from five to six months, so that the period itself did not seem to indicate any change, although further followup of these children for a longer period of time may indicate differences.

In table IV we have another way of looking at the data. Here, the over-all changes in each category are summed up. Thus, in the category of awareness of other children, 4 children showed marked improvement; 4 showed moderate improvement; and 6 displayed no change. None of the children became less aware or less remote than they had been before. There was a distinct increase in awareness, particularly of adults, and a lesser change in awareness of objects. A drive toward language was also noticed.

Two other items might also be mentioned: an increase in motor activity, which was dis-

TABLE IV

Results of Individual Items

Category	Number of children				
	++	+	0	−	−−
Awareness of children	4	4	6	0	0
Awareness of adults	7	5	2	0	0
Awareness of objects	1	6	7	0	0
Motor activity	1	10	2	1	0
Language	5	6	3	0	0
Reaction time	1	8	3	2	0
Anxiety	0	1	11	2	0
Pathologic symptoms	0	0	14	0	0
Affect	0	5	9	0	0
Relationship with other children	0	2	7	3	2
Relationship with adults	0	2	9	3	0

played by 11 of the children, and an increase, seemingly, in reaction to stimuli and demands.

CONCLUSION

Seven of the patients showed definite improvement; 3, slight improvement; and 4, no improvement.

This study was undertaken as a scouting expedition to determine the effectiveness of Marsilid in the treatment of autistic children. Of the 14 children observed, 10 showed some degree of improvement; in 7 of these 10, the improvement was rather definite.

This study was limited—this must be emphasized again—by the number of patients and also by the nature of the observations, which were purely clinical. This was not a controlled study. Six of the children were under intensive treatment at a day care center, and all the others were receiving some psychiatric attention. Thus, one may question whether the changes observed were due to the drug or to other influences.

However, all these children were suffering from a very serious chronic disorder in which improvement, if it does occur, is very slow. More than half were known to the author for a considerable period of time before the drug program began.

Knowledge about all these children was available from very early life, so that patterns of change or occasional spurts were quite apparent.

In surveying the group, it was evident that some change had taken place. The children had been stimulated and were more alert. They appeared to be scanning their environment rather than being completely indifferent to it. Parents reported that their children were more aware of them and watched what they were doing. In addition, some of the children responded to commands of direction for the first time in their lives. The increased awareness seemed to be centered principally upon adults and secondarily upon other children and upon objects; this is of interest because the pattern of withdrawal of children who begin to regress, say, at the age of 2, is first to lose contact with the surrounding environment, then with their parents, and then with themselves.

The language response has been most interesting. Three children in this group who had a comparatively considerable use of language at the start of the study showed little change in their stream of talk. What improvement was observed took place in those children who were completely mute or used very few words. In the former, an increase in babbling was first noticed. Then, in some children, an intense drive to communicate and to speak words was displayed. In one child, the picture seemed to be similar to that seen in children with infantile aphasia of the expressive type. This child, who had previously been mute, began to babble upon receiving Marsilid. Then he began pointing at things and appeared to be struggling to express himself. Finding it impossible to speak, he would become frustrated and storm about for a short period.

One child who had a very limited vocabulary, consisting essentially of "Mama" and "Dada," began adding new words and joining short words together, forming short phrases.

The children appeared to react more quickly to commands or to stimuli. Motor activity was generally increased. In certain instances, this was a source of difficulty. Generally,

the parents were willing to accept some increased activity, in view of the other changes taking place. In only 1 case was there very serious objection. The parents in this instance were particularly sensitive to the child's restlessness, which, however, did not exceed that seen in the other children.

Three of the children developed difficulty in sleeping while receiving Marsilid. They were reported as waking up at night and being unable to return to sleep. For these children, tranquilizing drugs were prescribed at night. In two instances, hydroxyzine hydrochloride,* and, in one, chlorpromazine hydrochloride† were administered and appeared to control this problem. The simultaneous use of tranquilizing drug and Marsilid did not appear to be contraindicated in 1 patient. In this instance, the child had been on chlorpromazine because, in addition to his autism, he demonstrated anxiety and restlessness. He was placed on Marsilid, and chlorpromazine was continued. This child displayed increased alertness, improvement in language and reaction time, and no objectional increase of motor activity; nor did the anxiety return.

Thus, the results of this scouting study appear to be that, within the limits of the study, Marsilid was a drug of particular promise in the treatment of autistic children. It is the only satisfactory stimulating drug for schizophrenic autistic children available at the present time. It appeared to have the special property of increasing the drives of the child, particularly toward other people and toward communication. Possibly, it stimulated purposive activity or striving aspects of the child's personality. It may be concerned with conation.

Of course, it is essential that the observations be confirmed by objective evaluation in controlled fashion. This series is recognizably small and must be extended. It is particularly hoped that this report will stimulate others to duplicate such studies. The objective evaluation would not appear to be too difficult, since we are dealing with many items that can be quantitatively studied. Language production and reaction time, for example, can be rather accurately measured.

It is noteworthy that Marsilid, which has been described as a euphoriant, failed to show any such action in the children. Well marked lightening of mood was not evidenced in any of the children and, where this effect was observed in lesser degrees, it seemed secondary to the general changes that were taking place.

There were no toxic changes observed in this series. Urinanalyses and blood cell counts were done frequently, and findings were invariably within the normal range. No change of muscle tone could be observed in the children receiving Marsilid.

No improvement in appetite was observed in any of the children. Several of the children had bizarre eating habits. One child, in particular, was on a diet so limited and deficient that he caused grave concern. We had hoped that, certainly, some improvement in appetite would take place. Unfortunately, no change in appetite was noted.

In two instances, children who had been constipated and suffered from impaction had temporary improvement in bowel motility.

The combination of Marsilid with other stimulating drugs, such as the amphetamines

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* The trade name of J. B. Roerig & Co. for hydroxyzine hydrochloride is Atarax.

† The trade name of Smith, Kline & French Laboratories for chlorpromazine hydrochloride is Thorazine.

described for adults, has not been attempted as yet, although it would appear to be worth a trial in those cases in which Marsilid is not effective.

SUMMARY

Fourteen autistic children, ranging in age from 4 to 10 years, were treated for two to six months on dosages of Marsilid ranging from 0.5 to 2.0 mg./pound.

Of the 14 children, 7 showed definite improvement; 3 slight improvement; and 4, no improvement.

The prominent changes were increased alertness, particularly in awareness of adults; drive for further development of language; increased motor activity; and increased reactivity.

The results are based upon clinical observations; no controls were used.

No toxic effects were observed in this study.

Within the limitations of this study, Marsilid appears to be of particular promise in the treatment of autistic children.

These results warrant further investigations, particularly those utilizing objective criteria of evaluation.

RESUME

Le Marsilid a été administré pendant 2 à 6 mois à 14 enfants affectés d'autisme. L'âge des enfants s'échelonnait entre 4 et 10 ans.

Les résultats du traitement par le Marsilid révèlent une nette amélioration chez 7 enfants, une amélioration légère chez 3 et l'absence d'amélioration chez 4. Les modifications prédominantes étaient l'éveil de l'attention (en particulier ils prenaient conscience de l'adulte), l'intérêt pour les moyens de communication verbale et l'accroissement de l'activité motrice et de la réactivité. Aucune réaction d'intolérance n'a été observée.

L'auteur déclare que le Marsilid est le seul médicament stimulant satisfaisant dont on dispose actuellement pour le traitement des enfants autistiques schizophrènes.

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Studies on the Gastrointestinal Effects of Marsilid*

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The following case stimulated our interest in the clinical effects of Marsilid† in gastrointestinal disease.

A 31 year old architect complained of weakness, diarrhea, abdominal cramps, fever, and progressive weight loss for several months. There was a history of onset of similar symptoms while the patient was a prisoner in a concentration camp in Germany thirteen years previously. He had received no treatment at that time, and his symptoms subsided spontaneously. However, shortly after coming to this country, he suffered several recurrent attacks, which led him to seek medical attention. In June 1955 the diagnosis of ileocolitis was established by gastrointestinal examination. Because of active inflammatory disease, which was not responsive to usual medical measures, an operation was performed in July 1955. Involvement of the small and large bowel was too extensive to permit resection, and an ileosigmoidostomy was performed to by-pass the affected area.

After surgery the patient improved and was able to resume part-time employment. However, the symptoms recurred eighteen months later. Despite treatment with bed rest, vitamins, phthalylsulfathiazole, neomycin, and antispasmodics, his condition continued to deteriorate. Steroids had not been used because of failure of response during an earlier exacerbation.

Physical examination showed a well developed white man with signs of evident weight loss and low-grade fever. Visible peristalsis was observed in the abdomen, which was tender in the right and left lower quadrants, but no masses were palpable. The scar of previous surgery was well healed. Meperidine,‡ 100 mg. every four to six hours, was required to control the abdominal cramps.

The patient was hospitalized and started on a course of intravenous ACTH, resulting in temporary appetite stimulation and euphoria, but no significant effect on the signs of inflammatory disease was noted. Marsilid therapy was then instituted, with a starting dosage of 100 mg. three times a day. The patient's weight at the beginning of therapy was 105 pounds. The dosage of Marsilid was tolerated without ill effects, and after three days it was increased to 200 mg. three times a day. Within the next seventy-two hours, abdominal cramps ceased, meperidine was no longer required, and appetite returned. Shortly thereafter, diarrhea subsided and weight began to increase.

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† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

‡ The trade name of Winthrop Laboratories for meperidine is Demerol.

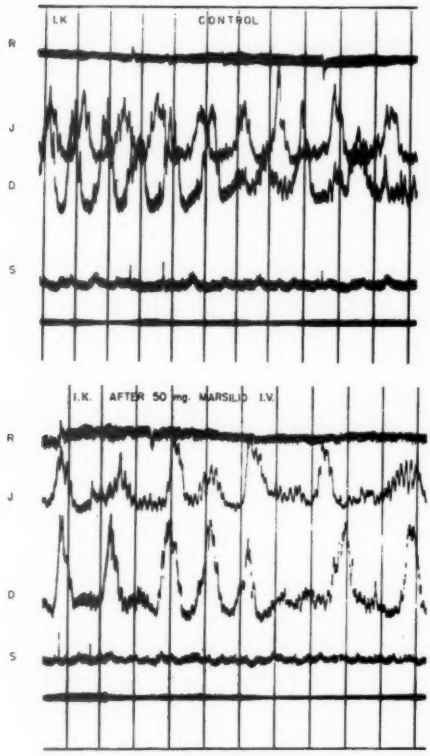

FIG. 1. Marsilid motility studies.

Dosage was reduced from 600 to 350 mg./day because of mild dizziness and transient heartburn. On the reduced dosage, abdominal cramps returned, and Marsilid was therefore increased to 650 mg./day, given as 150 mg. after each meal and 200 mg. at bedtime. The patient has been maintained on this dosage for approximately six months, during which time all signs and symptoms of inflammatory disease have disappeared and there has been a weight gain of 55 pounds.

The only significant side effects encountered, other than the very mild dizziness and heartburn, have been a loss of libido and disturbed dream content.

The literature contains no information concerning the effects of Marsilid on gastrointestinal functions. We are reporting herewith the results of our preliminary investigations of the effects of this drug on gastric secretion and gastrointestinal motility.

Figure 1 shows a sample record of motility recorded from the stomach, duodenum, and jejunum. The upper record represents a small portion of the control period, and the lower portion represents an eleven minute period shortly after the intravenous administration of

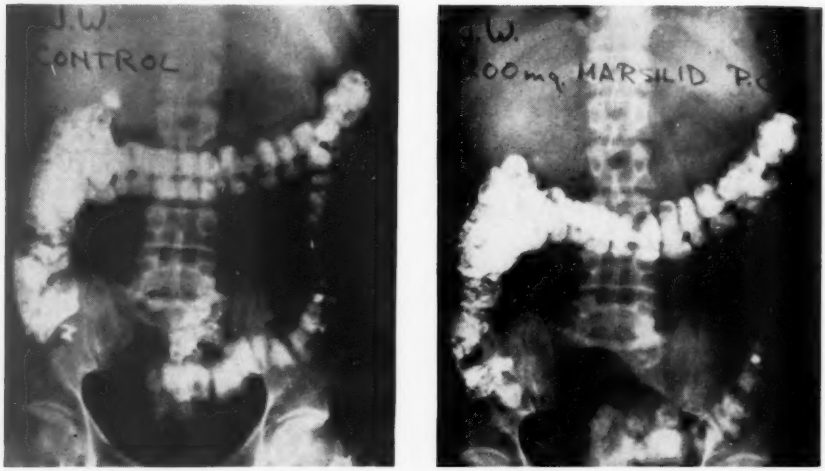

FIG. 2. Patient J. W. Left, October 17, 1957, control film; right, October 21, 1957, after patient had received 200 mg. of Marsilid orally.

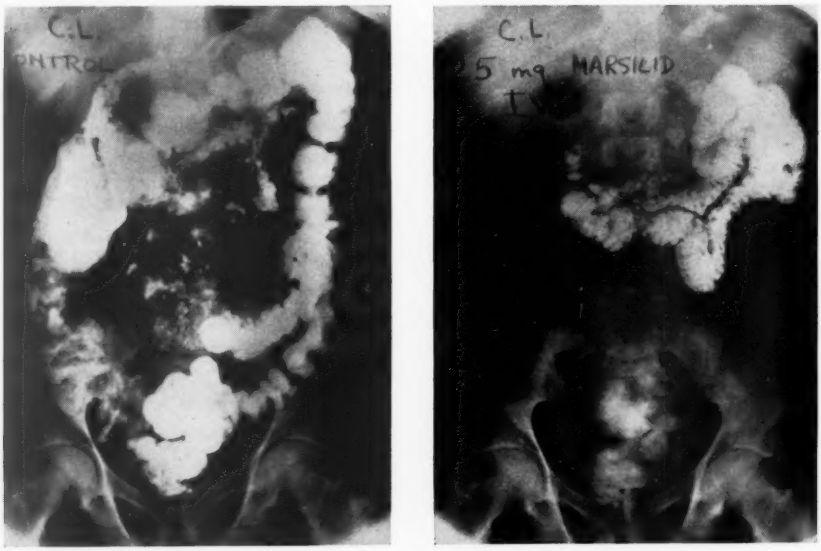

FIG. 3. Patient C. L. Left, November 6, 1957, control film; right, November 8, 1957, after patient had received 25 mg. of Marsilid intravenously. Barium in rectum is residual of control study.

50 mg. of Marsilid. There is a suggestion of diminished frequency of contractions. Of 6 patients studied by this technique, 2 demonstrated these suggestive changes.

The second method used for studying gastrointestinal motility was the measurement of barium transit time. We gave 200 mg. of Marsilid orally with the barium meal, took a six hour film, and compared it with the control film done on the same patient several days previously.

Figure 2 shows a typical study of 1 patient in whom the barium transit time was obviously unaltered, the barium reaching the rectum in both studies in six hours. On the left is the control film, and on the right a film of the same patient after he had received 200 mg. of Marsilid orally.

Of the 14 patients studied in this way, 13 demonstrated no significant effects. Some delay appeared to have occurred in 1. However, in a second group of 11 patients, 25 mg. of Marsilid was given intravenously at the time of the barium meal, and films were taken at three, six, and nine hours thereafter. These were also compared with the control studies.

In figure 3, the control study at the left shows that barium has reached the rectum in three hours, whereas the barium in the companion study is still within the jejunum after administration of 25 mg. of Marsilid intravenously. This is considered evidence of retardation of small bowel motility by Marsilid. It is suggested that this may explain the constipating action that is reported in some persons. Of 11 patients studied in this manner, 4 demonstrated this delay in the small bowel, 1 showed some delay after nine hours, and 6 demonstrated no difference.

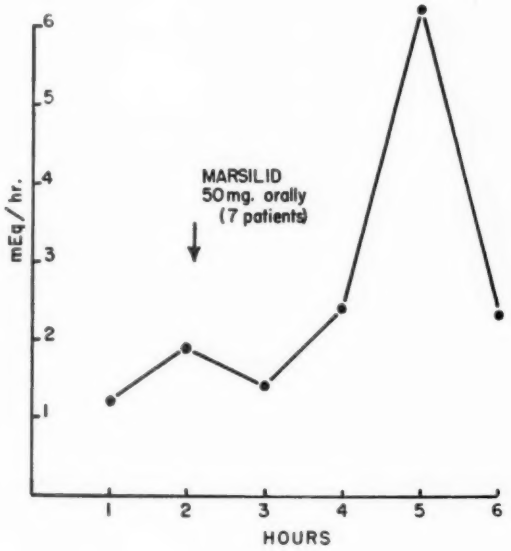

FIG. 4. An increase in acid output is demonstrated in 7 patients given 50 mg. of Marsilid orally. Each point on the graph represents an average of all patients studied.

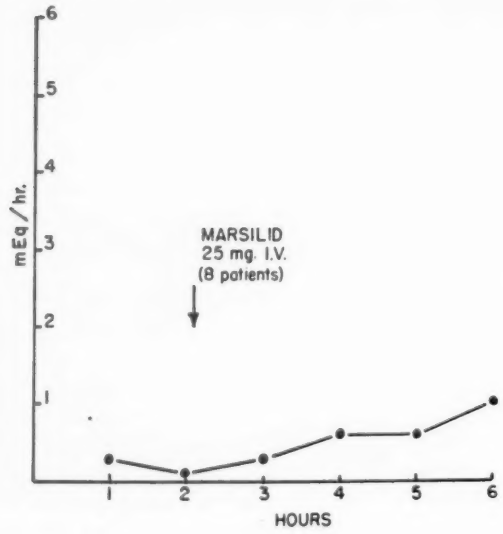

FIG. 5. In a second group of 8 patients who were given 25 mg. of Marsilid intravenously, secretory stimulation again is evident.

The effects on gastric acid secretion were studied by continuous gastric aspiration, employing fluoroscopic positioning of the tube and two hour basal control periods. Secretion was studied for four hours after administration of the drug. Results were translated into milliequivalents of acid secreted per hour.

Of 7 patients receiving 50 mg. of Marsilid orally, 5 showed a significant increase of acid output; the averages of the seven tests are plotted in figure 4. In the second group of 8 patients who were given 25 mg. of Marsilid intravenously, secretory stimulation occurred in 5; the average values are represented graphically in figure 5.

Additional studies were performed in 3 patients who were given 100 mg. of Marsilid orally, and very definite stimulation was demonstrated in 2. In the third, achlorhydria was noted during the control period, after Marsilid administration, and after histamine stimulation. In 2 patients who were achlorhydric during control periods, and to whom 25 mg. of Marsilid was given intravenously, there was no response.

CONCLUSIONS

Our preliminary data suggest that the constipating effect of Marsilid may be a result of inhibition of small bowel motility. The effect on the colon has not been studied. In addition, gastric secretory stimulation appears convincingly demonstrated.

The physiologic basis for dramatic clinical improvement in a patient with far advanced ileocolitis receiving massive doses of Marsilid is purely speculative. The improvement occurred rapidly and has been sustained for six months.

RESUME

Dr. Brody rapporte ses recherches expérimentales sur les effets du Marsilid sur la motilité gastro-intestinale et les secrétions gastriques.

Le Marsilid a causé une inhibition de la motilité gastro-intestinale légère, mais significative, et une tendance au péristaltisme intestinal de type I chez 2 sujets parmi les 6 dont la motilité intestinale a été enregistrée. Sur un nombre de 14 malades ayant reçu le Marsilid avec le repas baryté, il n'y eut aucune variation dans la durée du transit chez 13 d'entre eux; un certain délai fut observé chez 1 malade. Parmi 11 malades auxquels le Marsilid a été donné par voie intra-veineuse au moment du repas baryté, 4 ont présenté un retard d'évacuation appréciable; dans un cas le retard a été de neuf heures et dans six aucune différence appréciable n'a été observée.

A l'égard des secrétions gastriques, les sujets qui reçurent 50 mg. de Marsilid oralement ont présenté une augmentation notable de la secrétion acide. Dans le groupe où le Marsilid a été administré par voie intraveineuse, la stimulation de la secrétion a paru un peu plus définie. Une stimulation marquée a été décelée chez 2 sujets sur les 3 qui avaient reçu 100 mg. par voie buccale.

Les données préliminaires suggèrent que l'action constipante du Marsilid peut résulter d'une inhibition de la motilité de l'intestin grêle. La stimulation de la muqueuse gastrique après administration orale ou intraveineuse de Marsilid paraît inconstablement démontrée.

The Effect of Marsilid on Blood Pressure in Hypertensive Patients

*Jack Harnes, M.D.**

NEW YORK, NEW YORK

Marsilid† has been reported to have a hypotensive effect on hypertensive patients. In view of the difficulties encountered with available effective hypotensive agents, a trial of Marsilid was initiated in a group of patients with hypertension.

METHODS

Marsilid was given orally in divided doses to a group of 17 patients with essential hypertension. Blood pressures were taken twice weekly, weekly, and less frequently, depending on the condition and cooperation of the patient. Two blood pressures were taken with the patient in the standing position and two in the supine position after the patient had been in that position for at least three minutes. The pressures in each position were then averaged separately and graphed. Most of the patients had had prolonged control blood pressure determinations while receiving other ineffective and placebo therapy. A placebo in place of Marsilid was used whenever a hypotensive effect was believed to have been produced. When the pressure reached pretreatment levels, Marsilid was substituted for the placebo to confirm the original observation. The initial dose varied considerably, but at present 50 mg. are given initially four times a day. The maximum doses that the patients took, and the apparent maintenance doses are shown in table I.

RESULTS

The results are shown in table I. The drug produced a definite orthostatic, hypotensive effect in 15 of the 17 patients to whom it was administered. In 2 patients, side reactions appeared before any hypotensive effect was noted, and administration of the drug was stopped. A delay was noted in the production and loss of the hypotensive effect when the drug was started and withdrawn. This has resulted in some difficulty in determining the proper maintenance dose.

The major effects in lowering blood pressure were noted when the patient was in the standing position. In 5 patients, however, a lowering of the pressure seems to have occurred with the patient in the supine position.

The side reactions are listed in table II. In the 2 patients in whom the drug was ineffective, the side effects were sufficiently severe to warrant withdrawing the drug. In the

* From the Hypertension Clinic III, (New York University) Medical Division, Bellevue Hospital, New York, New York.

† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

other patients, the reactions occurred primarily with maximum doses, and at maintenance doses they did not seem sufficiently severe to cause the patient to stop taking the drug.

A sufficient period of observation has not elapsed to evaluate the possibility of tolerance developing to the drug.

TABLE I

Results of Marsilid Therapy

Patient No.	Sex	Age (years)	Weight (pounds)	Maximum Dose (mg.)	Hypotension (orthostatic)	Hypotension (supine position)	Apparent Maintenance Dose (mg.)	Side Reactions and Comments
1	M	41	130	200 t.i.d.	0	0		Drunkenness; medication stopped without adverse effect
2	F	40	171	100 t.i.d.	+			Orthostatic effect present after twenty days; patient did not return to clinic
3	F	72	148	50 q.i.d.	+	0	50 daily	Faintness, drowsiness, drunkenness
4	F	62	140	100 q.i.d.	+	0	100 t.i.d.	Faintness, dry mouth, nausea, tremor at bedtime
5	F	38	155	200 q.i.d.	+	0	150 q.i.d.	Drowsiness
6	F	50	231	100 q.i.d.	+	0	50 q.i.d.	Faintness
7	F	47	125	250 q.i.d.	+	0		Minimal orthostatic effect, drowsiness, insomnia, drunkenness, nightmares
8	M	64	190	50 t.i.d.	+	0	75 daily	Faintness several times
9	M	69	195	100 t.i.d.	+	+	100 t.i.d.	No effect on persistent angina
10	F	49	190	100 q.i.d.	+		100 q.i.d.	Occasional faintness
11	F	65	149	50 q.i.d.	+		50 t.i.d.	Dry mouth, drunkenness
12	F	65	172	100 q.i.d.	+	+	50 q.i.d.	Faintness
13	M	64	142	150 t.i.d.	0	0		Faintness, drunkenness
14	F	45	125	100 t.i.d.	+	+	50 t.i.d.	Tremor
15	F	55	175	150 q.i.d.	+	+	100 q.i.d.	Faintness, drowsiness
16	F	60	151	100 t.i.d.	+	+	50 q.i.d.	Faintness
17	M	40	170	100 q.i.d.	+		50 t.i.d.	Impotence

TABLE II

*Side Reactions of Marsilid**

Side Reactions	No. of Patients
Faintness	9
Drunkenness	5
Drowsiness	4
Dry mouth	2
Tremor	2
Insomnia	1
Nightmares	1
Nausea	1
Impotence	1
Constipation	1

* 17 patients studied.

CONCLUSIONS

Oral administration of Marsilid had an orthostatic, hypotensive effect on 15 of 17 patients with hypertension. The side reactions that occurred with large doses were not prominent when maintenance doses were given.

RESUME

Le Dr. Harnes rapporte ses observations sur l'emploi du Marsilid chez 17 patients atteints d'hypertension essentielle. Une posologie adaptée à chaque cas a été appliquée. Le Marsilid a été donné par voie orale. La dose maxima a été de 200 mg. cinq fois par jour. La dose initiale usuelle était de 50 mg. quatre fois par jour. La tension artérielle était déterminée chez le malade debout ou couché. Quand l'effet d'hypotension s'était manifesté, un placebo était substitué au Marsilid. A mesure que la tension artérielle retournait au niveau antérieur au traitement, on reprenait l'administration du Marsilid. La réduction de la tension artérielle durant la cure de Marsilid a confirmé l'observation originale d'une activité hypotensive de la drogue.

Le Marsilid a produit une hypotension orthostatique chez 15 des 17 patients observés. Dans 5 cas sur 15, la baisse de la tension artérielle s'est également produite chez le malade couché. Les réactions secondaires qui se produisent avec les doses élevés du médicament ne sont pas notables avec les doses d'entretien.

Discussion

DR. HARVEY E. NUSSBAUM:* At St. Barnabas we studied the effect of Marsilid in a

* Attending Cardiologist and Chief of the Cardiac Clinic, St. Barnabas Hospital, Newark, New Jersey.

manner similar to that presented by Dr. Harnes, and we obtained similar results. Twenty-two of the patients have been receiving Marsilid long enough to permit proper evaluation. Of these 22, 17, or approximately 77 per cent, responded to treatment. Of 5 who did not respond, 1 had syphilitic aortitis, 2 are now considered to have had insufficient dosage to respond, and 1 had had a sympathectomy, but was still hypertensive and ultimately proved to be unresponsive to most of the ganglionic blocking agents as well. The fifth patient showed no response, although he was receiving what was considered an adequate dose.

The average dose was 50 mg. three times a day. When the dosage fell below this level, it was definitely found that the patients tended to become less responsive. All patients who responded did so on a minimal dose of 100 mg. a day. Below this dose, Marsilid was ineffective. However, even when low doses were given, a beneficial effect on mood was exhibited. At the dosage level employed, there were few side effects. The commonest

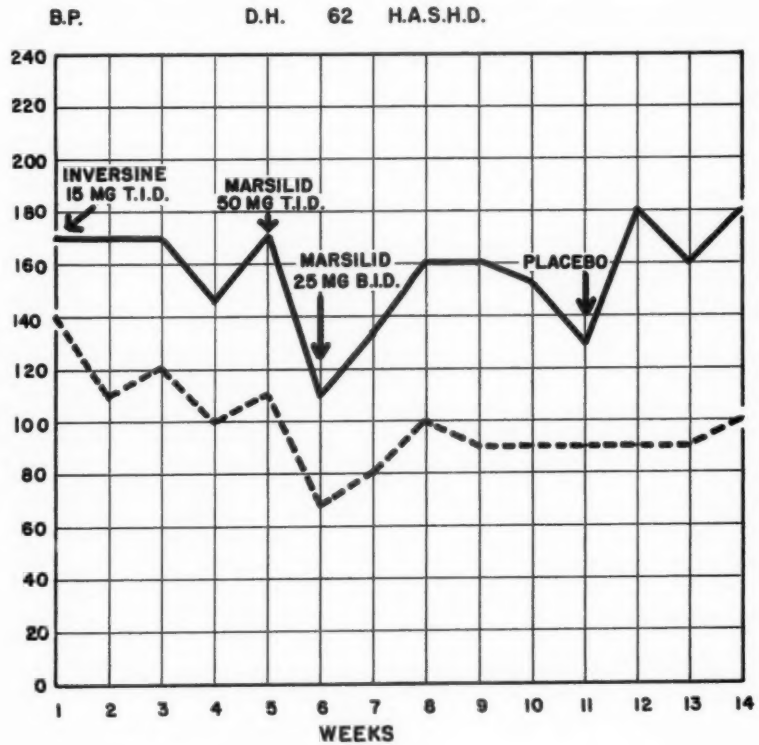

FIGURE 1.

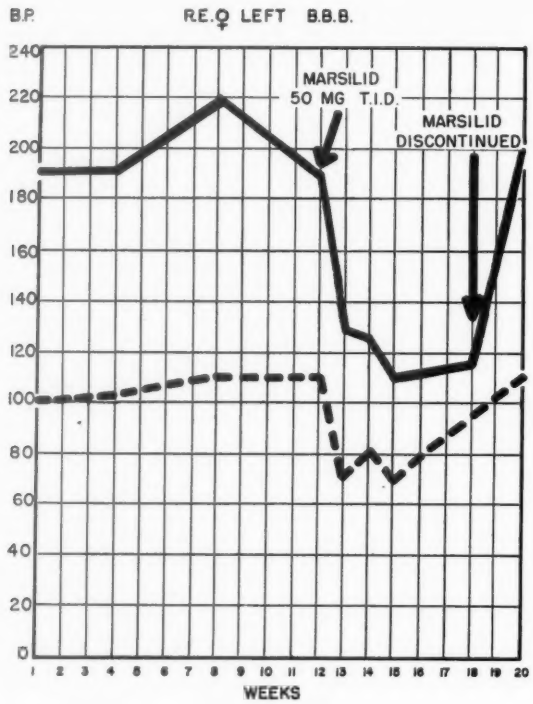

FIGURE 2.

side effect was vertigo, and it was found in more than 50 per cent of the patients, but it was never severe enough to warrant discontinuing of the drug.

It is noted with interest that Dr. Harnes reports that 1 patient became impotent while receiving the medication, and other contributors to the symposium have noted this side effect. We had 1 patient who became impotent while receiving ganglionic blocking agents, but when he was given Marsilid quite the opposite occurred, so much so that he was troubled enough to complain about it.

Acquired tolerance to the drug was not observed. After eight months, the drug was still effective at the same dosage level. We have seen no evidence of either hepatic or renal toxicity.

Several representative cases are illustrated in figures 1 to 6. Most of our patients have been the subject of prior studies on ganglionic blocking agents and other agents. One patient (fig. 1) had been taken off mecamylamine,* which he had been receiving in doses of 15 mg. three times a day. Using a base blood pressure of 170/140 without medication,

* The trade name of Merck Sharp & Dohme for mecamylamine is Inversine.

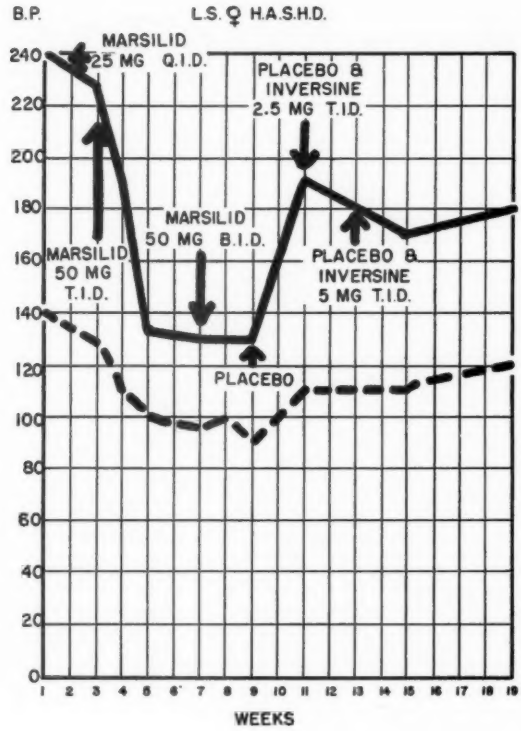

FIGURE 3.

and a pressure of 150/100 while he was receiving mecamylamine, he was given Marsilid when the blood pressure was 170/100; a precipitous drop to 110/70 occurred. At this point, the dosage was lowered and the pressure increased somewhat.

All these studies were done using placebos and a double blind technique, so that we were unaware at which point the placebo was given. The placebo was given when the blood pressure was 130/90, and there was a prompt rise in the pressure to between 160 and 180, without a great rise occurring in the diastolic pressure.

Figure 7 represents a patient who had rheumatic heart disease and hypertensive heart disease. This patient was placed on 50 mg. of Marsilid three times a day when his blood pressure was approximately 190/120 and the pressure went down to 130/80; unknown to us, the placebo was given at a time when the pressure seemed to be rising, and there was a rise in pressure to 210/130. At fourteen weeks, 50 mg. of Marsilid were given, twice a day, and a hypotensive effect was produced.

Figure 8 represents a 48 year old patient with hypotensive heart disease who had a blood pressure of approximately 220/120. When the patient was receiving 50 mg. of Marsilid

three times a day, a tremendous hypotensive effect was shown. Again the placebo was given at a point at which the pressure seemed to be rising, and the effect of the placebo on the blood pressure can be seen.

DR. CESARMAN: All the patients with angina pectoris studied by us in Mexico were studied concurrently for effects on blood pressure, and I think we have had fairly extensive experience in studying effects of Marsilid on blood pressure. We believe that our results were similar to those that have been presented. But we have also seen that the blood pressure of a normotensive patient falls as well, and sometimes goes down so much that patients in the upright position have blacked out, a condition that we have been unable to control even by using a tight girdle and elastic stockings, which were usually employed for patients who had a sympathectomy.

It was also found that this effect is slow to appear and slow to disappear. One of our patients, a normotensive patient with angina, blacked-out several times when he stood up. We had to put him to bed and gave him a girdle and stockings, but even with these measures

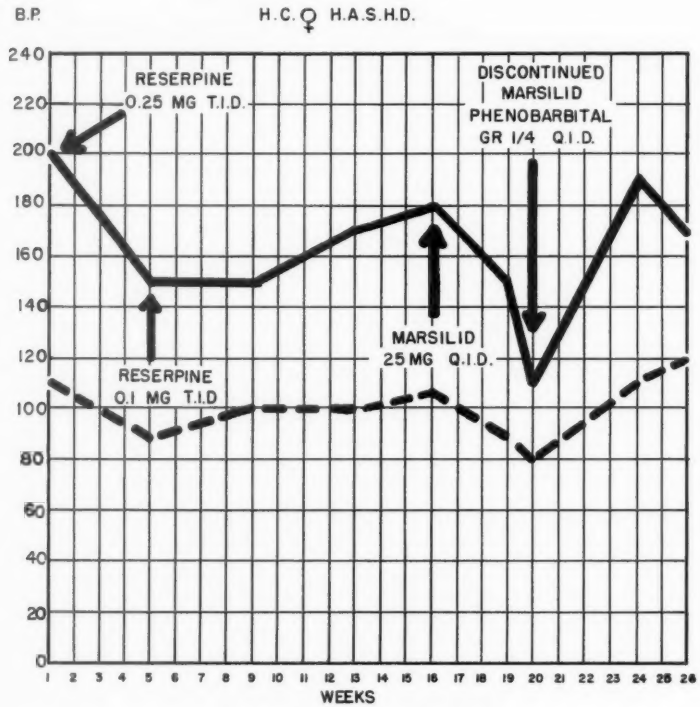

FIGURE 4.

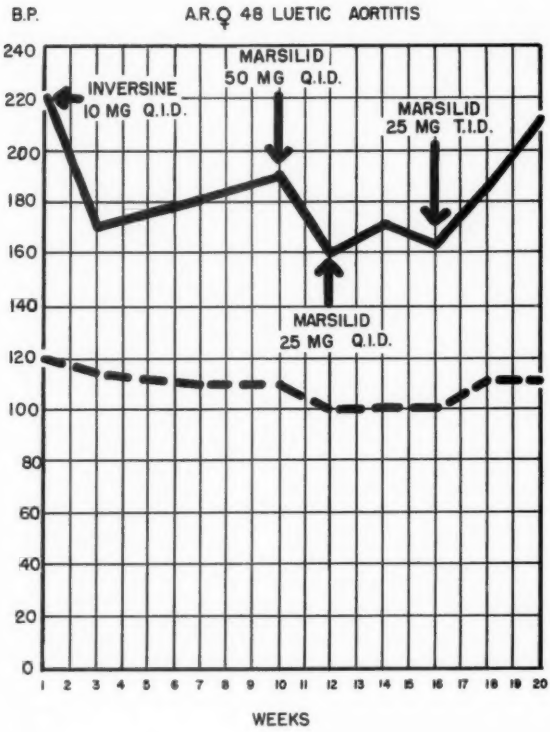

FIGURE 5.

the blood pressure went down every time the patient sat up. The effect on this patient lasted almost four weeks, so we believe that Marsilid acts as a ganglionic blocking agent, although not directly. It may act either through a metabolite, or by inducing or producing the appearance in the blood of another substance, which would be the ganglionic blocking agent.

There are other side effects that have been reported, such as dryness of the mouth and constipation, which also make us believe this is ganglionic blocking activity. The sexual impotence reported by many and seen also by us is the same type of effect encountered with the use of ganglionic blocking agents, and of the same type as is seen in persons having undergone sympathectomies.

We have not seen any patients in whom the libido improved or who had a greater capacity for erection. At the beginning of therapy, some patients were unable to have an orgasm, although they were capable of erection. In other words, impotence also develops. One of the patients complained about the anginal pain, but then said he preferred the angina to sexual impotence, so the medication was stopped.

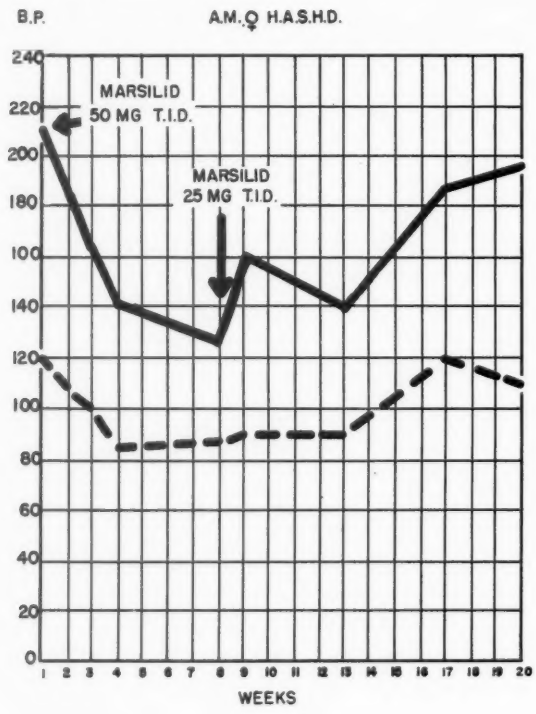

FIGURE 6.

DR. ROBIE: A patient of mine, a woman, had had a number of courses of electroshock therapy for severe depression. She had been in and out of a mental hospital several times. When treated by me for about a year and a half, she was maintained on electroshock therapy given every two or three weeks. When Marsilid came along, I was anxious to try it on her. I gave her the drug and, except for the complication of some edema, the results were very successful.

The patient is married to an impotent man, but she has a high sexual drive and has complained about this on frequent occasions. In her case, Marsilid reduced her libido. She is now quite content to live with an impotent man, and is not disturbed by it.

DR. FRIEND: I would like to make a comment on paralysis of the bladder and bowel. With the use of ganglionic blocking agents, the parasympathetic as well as the sympathetic ganglia are paralyzed. If we had an agent that would stimulate the parasympathetic ganglia of the autonomic nervous system, the blood pressure would not be increased but many of these untoward reactions would be corrected.

In this regard, we used ambenonium,* which is a powerful cholinergic stimulant. Urologists tell me that it is the most potent agent available for restoring the bladder to normal in the presence of ganglionic blocking agents. By the same token, the bowel becomes more active.

We had a patient who was receiving a ganglionic blocking agent in the form of mecamylamine. He was troubled with impotence but, after receiving ambenonium, he no longer had this difficulty. This leads me to believe that perhaps we should consider drugs like neostigmine, ambenonium, and other cholinergic stimulants for overcoming some of these side effects. It may be that, in this way, impotence can be improved considerably.

DR. MARKS: Dr. Harnes said he encountered some side effects that he did not believe were attributable to the hypertension. He mentioned dizziness as one of them. I wonder if I might ask him whether or not he has determined the blood sugar levels on these patients?

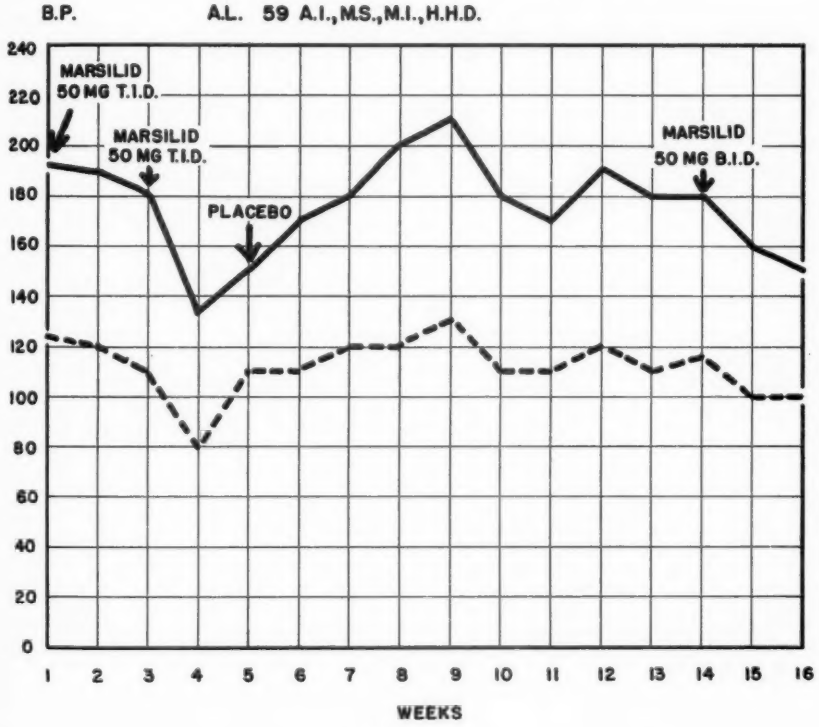

FIGURE 7.

* The trade name of Winthrop Laboratories for ambenonium chloride is Mytelase.

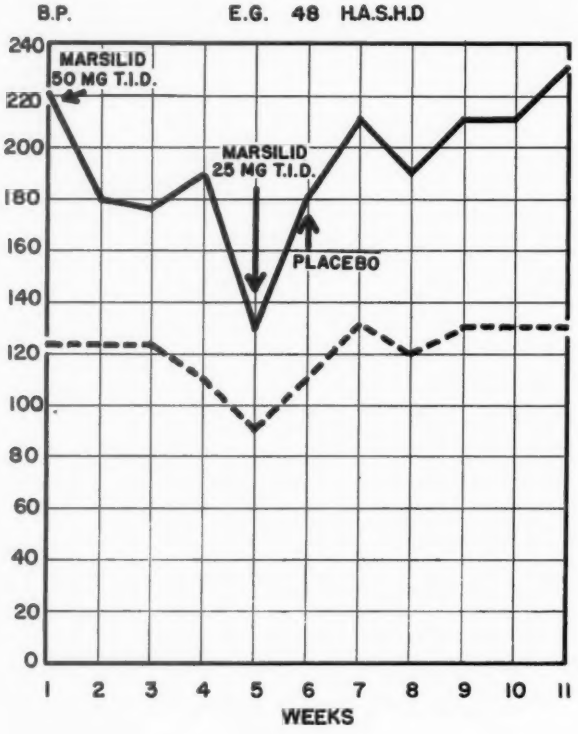

FIGURE 8.

In original reports on the use of Marsilid in patients with pulmonary tuberculosis, the blood sugar levels were found to have dropped considerably, and this fact might be a possible explanation of some of Dr. Harnes' findings.

DR. HARNES: Those patients were not tested for blood sugar levels.

Biochemical and Pharmacologic Actions of Marsilid on the Heart

A. Pletscher, M.D., Ph.D., and B. Pellmont, M.D.*

BASLE, SWITZERLAND

It has been found that isopropyl isonicotinic acid hydrazide, Marsilid,† a compound that inhibits monoamine oxidase[1–4] is of value in the treatment of angina pectoris.[5] In this connection two findings are of interest. First, the clinical effect appears three to ten days after daily administration of 150 mg. of the drug. If the medication is stopped, the pain reappears after three to ten days. Second, isonicotinic acid hydrazide, isoniazid,‡ a compound closely related to Marsilid, does not seem to have a therapeutic effect in persons with angina pectoris.

In guinea pigs, Marsilid causes a marked rise, dependent on the dosage, in the catecholamine content of the heart. The maximal rise in the catecholamines is reached about sixteen hours after intraperitoneal administration of 100 mg./Kg. of Marsilid, and the catecholamine content remains elevated for at least 120 hours. Isoniazid, a compound that is a weak monoamine oxidase inhibitor,[6, 7] causes a significantly less marked rise of the catecholamines than does Marsilid (figs. 1 and 2).[8] The catecholamines in the heart, which consist mainly of norepinephrine, were determined by a spectrophotofluorimetric method.[9]

It may be seen that there exists a certain correlation between biochemical and clinical findings. Marsilid, a compound that causes a marked rise of the catecholamine content in the animal heart, has a therapeutic effect in angina pectoris. For isoniazid, a compound that causes less marked rise of the catecholamines, this does not seem to be the case. Furthermore, the beneficial effect of Marsilid lasts for several days after the medication is stopped; in addition, the onset of clinical action of the drug is slow. These properties are possibly connected with the long-lasting effect of one dose of Marsilid on the catecholamine content of the heart and with the resulting cumulative action of the drug.

It cannot be decided if the beneficial effect of Marsilid in angina pectoris is the direct consequence of the increased amount of catecholamines in the myocardium. Such an assumption would be in contrast with the views of Raab,[10] who thinks that catecholamines have a deleterious effect in angina.[10] Another explanation for the beneficial clinical effect of Marsilid may lie in the possibility that Marsilid inhibits the release of stored norepinephrine or the formation of a harmful norepinephrine metabolite in the heart. Both these possibilities would be consistent with our finding of an increased content of total norepinephrine in the heart.

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* Director, Medical Research Department, F. Hoffmann-La Roche & Company, Ltd., Basel, Switzerland.

† Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

‡ The trade name of Hoffmann-La Roche, Inc. for isoniazid is Rimifon.

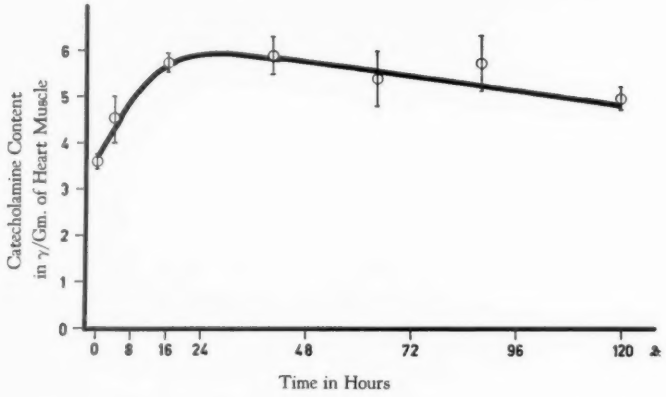

FIG. 1. Catecholamine content in the heart of guinea pigs after intraperitoneal injection of 100 mg./Kg. of Marsilid at zero time. Each point represents the average of 5 to 32 determinations. Vertical lines represent standard deviation.

Our first results on the pharmacologic action of Marsilid on the mammalian heart are summarized in figures 3 through 7. In the isolated perfused heart (figs. 3 and 4) Marsilid causes an increase of the coronary flow. With small doses (perfusion with Marsilid) the amplitude of the heart rate is moderately increased, whereas with higher doses (injection of Marsilid) a marked decrease of the amplitude can be seen. The frequency of the heart rate is not affected by Marsilid. Isoniazid in doses equimolecular to Marsilid definitely has

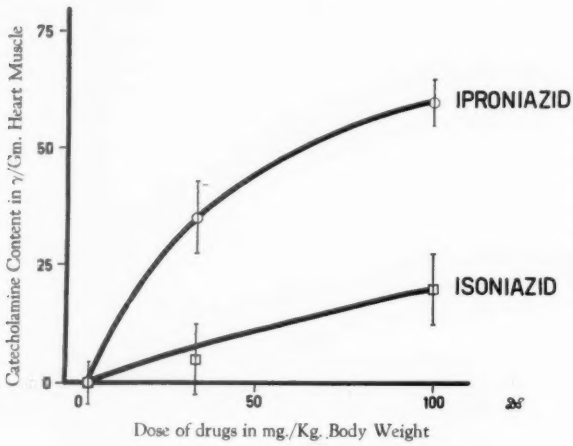

FIG. 2. Catecholamine content in the heart of guinea pigs 16 hours after intraperitoneal injection of Marsilid and isoniazid, respectively. Each point represents the average of 5 to 32 determinations. Vertical lines represent standard deviation.

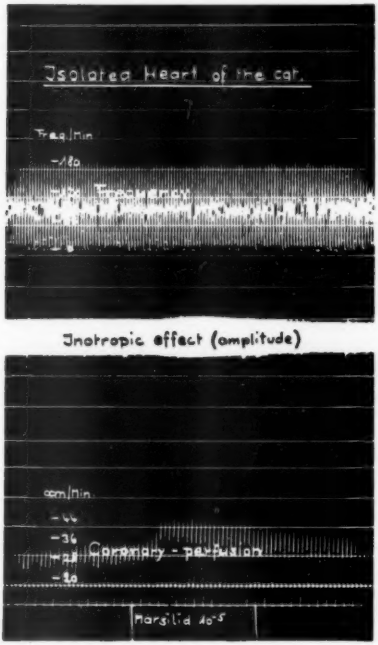

FIG. 3. Action of a perfusion of 10^{-5} Gm./ml. Marsilid on the isolated heart of a cat. Lower tracing, coronary perfusion flow; center tracing, amplitude of the heart; and upper tracing, frequency of the heart.

a lesser effect on coronary flow. The amplitude of the heart rate is markedly increased even with high doses of isoniazid whereas the frequency remains unaffected. The action of norepinephrine and a xanthine derivative is different from that of iproniazid. These two drugs not only cause an enhanced coronary flow but also a marked increase of amplitude and frequency of the heart rate.

In the heart *in situ* (fig. 5 through 7), Marsilid also increases the coronary flow. Similarly, the blood flow in the femoral artery is enhanced. The pressure in the left ventricle and in the femoral artery drops almost immediately after intravenous administration of Marsilid, but the pressure in the right auricle is not affected. Again, norepinephrine has a different pattern of action from that of Marsilid. The hormone increases the intraventricular, the intrafemoral and, to a certain extent, the intra-auricular pressure.

The pharmacologic findings described lead to the following conclusions. (1) It is unlikely that the pharmacologic actions of Marsilid are due merely to an enhancement of the effect of endogenous norepinephrine on the heart. The actions of norepinephrine and Marsilid differ from one another. (2) The finding that Marsilid lowers the amplitude of the isolated perfused heart raises the question of whether or not the action of the drug in angina pectoris is due to a negative inotropic effect. It is known that cardiac decompensation causes relief of anginal pain. Experiments with the heart *in situ*, however, do not support this

hypothesis. The fall in intraventricular blood pressure after intravenous Marsilid administration can be explained by a decreased peripheral resistance. Furthermore, the finding of unchanged intra-auricular pressure after intravenous Marsilid administration does not suggest the presence of a considerable negative inotropic effect.

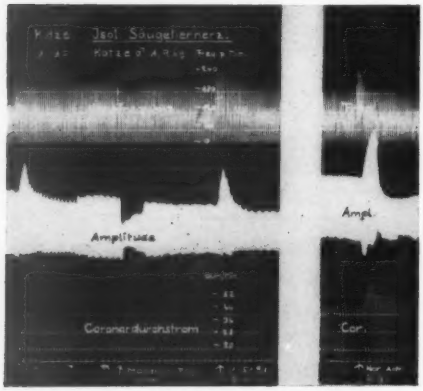

FIG. 4. Action of Marsilid, a xanthine derivative, and norepinephrine on the isolated perfused cat heart. The drugs were injected into the perfusion fluid (Locke's solution) within thirty seconds. Lower tracing, coronary perfusion flow; center tracing, amplitude of the heart; and upper tracing, frequency of the heart.

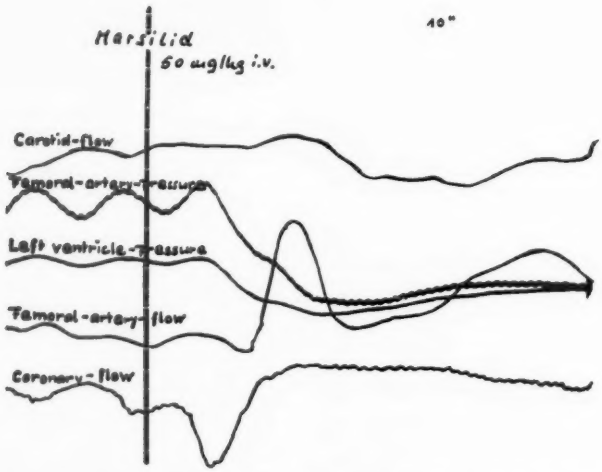

FIG. 5. Action of Marsilid on the coronary, femoral, and carotid flows as well as on the intraventricular and intrafemoral pressures of the rabbit *in situ*. A definite increase of the coronary flow after a short initial drop is to be seen. The femoral flow increases, too, whereas the carotid flow does not change significantly. The intraventricular and intrafemoral pressures drop markedly.

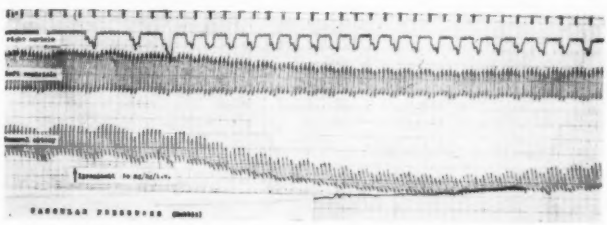

FIG. 6. Action of Marsilid on intra-auricular, intraventricular, and intrafemoral pressures of the rabbit *in situ*. The intra-auricular pressure does not change, whereas the intraventricular and the intrafemoral pressures drop markedly.

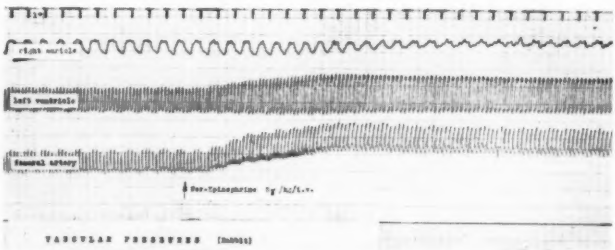

FIG. 7. Action of norepinephrine on intra-auricular, intraventricular, and intrafemoral pressures of the rabbit *in situ*. The intraventricular and intrafemoral pressures increase markedly; the intra-auricular pressure also shows a slight rise.

The pharmacologic effects of Marsilid have a rather acute onset, whereas the actions of this drug in angina and on the catecholamine metabolism are rather chronic. Further investigations are needed to elucidate whether there is any connection between these biochemical and pharmacologic findings and the clinical effects of the drug.

SUMMARY AND CONCLUSIONS

Marsilid, a drug with beneficial action in angina pectoris, causes a long-lasting rise in the catecholamine content of the heart of guinea pigs. Some parallels between the clinical and the biochemical actions of the drug suggest that the action of Marsilid in angina pectoris may be due, in part, to its effect on the catecholamine metabolism in the heart. However, the pharmacologic action of Marsilid on the isolated perfused heart, as well as on the heart *in situ*, cannot be explained merely as an enhancement of the effect of endogenous catecholamines. It also seems unlikely that Marsilid exerts its effect in angina by a negative inotropic action on the heart.

RESUME

Ces investigateurs ont constaté que le Marsilid (iproniazide), médicament possédant une activité favorable dans l'angor pectoris, produit une élévation prolongée de la teneur en catécholamine du coeur de cobaye.

Un certain parallélisme entre les activités chimiques et bio-chimiques de la drogue suggère que l'action de l'iproniazide, chez les sujets affectés d'angor pectoris, dérive en partie de son effet sur le métabolisme de la catécholamine au niveau du coeur. Toutefois, l'action pharmacologique de l'iproniazide sur le coeur isolé perfusé, de même que sur le coeur *in situ*, ne peut être simplement interprêté comme l'amplification d'un effet sur les catécholamines endogènes. Il semble improbable que l'iproniazide exerce son effet dans l'angor pectoris par une action inotrope négative sur le coeur.

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Marsilid in the Treatment of Angina Pectoris

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In his book, "The Way of an Investigator," Walter B. Cannon[1] includes a chapter under the title "Gains from Serendipity."† He uses this unusual word to designate the phenomenon of accidentally finding something different from that which was being searched for. This paper deals with a new case of serendipity.

On May 3, 1957, we began administering Marsilid‡ as a nervous stimulating agent to a group of cardiovascular patients from our private practice. One of them, suffering from severe effort angina and angina decubitus of eight years' duration, consumed an average of 20 nitroglycerin tablets daily and had received all known treatment except I^{131}; due to the limitations imposed by the relationship between effort and pain, he was physically incapacitated. To our astonishment, he informed us that, after five days of Marsilid therapy, he noted considerable reduction in the number of attacks. At the end of eight days, the anginal symptoms had completely disappeared, permitting him for the first time in many years to perform all types of effort, climb stairs, and walk as long a distance as one mile without pain and with only tiredness of the legs. We were surprised by this effect but did not quite realize at the time what was happening until we made the following observations: eight days after he had stopped taking Marsilid, the symptoms returned with progressive severity. When we again prescribed the drug, the symptoms disappeared after three days of therapy. We knew then that we had observed an unusual effect. A medication with known tuberculostatic properties[2] that had been rejected as more toxic than isoniazid[3, 4] and that had been revived at lower doses as an antidepressive agent,[5, 6] seemed to offer new and outstanding possibilities. We then initiated the treatment in other patients with severe angina in order to ratify or rectify our observations; in 72 consecutive cases we reencountered the same amazing results. This paper reports our observations in these first 72 cases.

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† "In 1754 Horace Walpole, in a chatty letter to his friend Horace Mann, proposed adding a new word to our vocabulary, 'serendipity.' The word looks as if it might be of Latin origin. It is rarely used. It is not found in the abridged dictionaries. . . . Walpole's proposal was based upon his reading of a fairy tale entitled The Three Princes of Serendip. Serendip, I may interject, was the ancient name of Ceylon. 'As their highnesses traveled,' so Walpole wrote, 'they were always making discoveries, by accident or sagacity, of things which they were not in quest of.' When the word is mentioned in dictionaries, therefore, it is said to designate the happy faculty, or luck, of finding unforseen evidence of one's ideas or, with surprise, coming upon new objects or relations which were not being sought."

‡ Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

METHODS AND MATERIALS

We selected from our files 72 patients with the diagnosis of severe angina pectoris, with pain on slight effort and with angina decubitus, with a daily consumption of over 4 nitroglycerin tablets, who had been treated with all known medical therapeutic measures for angina with the exception of I^{131} or surgical revascularization. All patients revealed abnormal findings in the electrocardiogram, and 8 gave positive results to the Master test. We did not perform the exercise test in the remainder of the patients because we thought it would be dangerous due to the severity of the symptoms and because the clinical diagnosis was obvious. The group was composed of 60 men and 12 women between 28 and 72 years of age, who had histories of angina ranging from one to eight years. Twenty-two of the patients had suffered myocardial infarction, and in 9 of these there was clinical and electrocardiographic evidence of two myocardial infarctions. The group included 12 patients with hypertensive heart disease, 7 patients with diabetic heart disease, and 3 patients with syphilitic heart disease.

Two of the patients had been accepted for surgical revascularization, and 1 had been returned from the operating room because of the development of arrhythmia and ischemia, registered electrocardiographically during induction of anesthesia. All previous medication was stopped, including hypotensive agents, and only cardiac failure and diabetes were treated in the usual manner when necessary.

No special diet was prescribed, and the patients were told that they could be as active as their pains would permit. The diagnosis of angina pectoris was based on clinical data, and the response to nitroglycerin; in all of them the electrocardiogram suggested coronary disease. The blood pressure was recorded weekly, and in 12 the blood picture was studied every two weeks. A daily record was kept of the frequency and intensity of the pains and of the capacity of effort to the point of eliciting pain, dyspnea, or fatigue. Also, the daily need for nitroglycerin was investigated. We recorded the side effects on the digestive and urinary systems and on the locomotive and central nervous systems. A weekly electrocardiogram was recorded in each of the patients, and an exercise test was registered after fifteen days of treatment. The dosage administered, regardless of weight or age, was 150 mg./day, divided in three doses of 50 mg. each. In 10 patients, the drug was stopped in order to find the duration of action. In 6, the dosage was diminished to investigate the smallest effective dosage. No information was given to the first 20 patients about the purpose of the drug in relation to angina. They were told, when they asked, that it was prescribed as a stimulating drug. The remainder knew that it was given to treat the angina, with no special emphasis on its action.

CLINICAL RESULTS

All of the patients experienced complete remission of clinical symptoms and restoration of the capacity for effort.

The duration of treatment varied between eighteen days and six months. The initial response appeared between three and ten days, and the total response between four and

twelve days. The daily dosage was 150 mg. The dosage per kilogram of body weight varied between 1.6 and 3 mg. daily, with an average of 2.3 mg.

The daily need for nitroglycerin diminished gradually during the first three days and rapidly during the next five; it disappeared completely when the total response was reached.

In the 10 patients in whom the medication was interrupted, we observed return of the symptoms between the third and eighth days. In all 6 patients in whom the dosage was reduced to 75 mg/day, we observed recurrence of symptoms, although they were not as severe as before.

ELECTROCARDIOGRAPHIC RESULTS

Although the detailed electrocardiographic findings will be reported in a later paper, the following information can be given here.

Exercise Test (Master Two-Step Tolerance Test). In 8 patients, results of the exercise test were positive before treatment. In 5, they were positive even without a special exercise test, as the effort of climbing on to the examination table was enough to elicit pain and produce electrocardiographic changes.

Case 1. A 62-year-old woman four years earlier had had an acute attack of coronary thrombosis with collapse and was kept in bed for six weeks. She had a history of slightly high blood pressure (170/100 mm.Hg.) and positive results were obtained from the Exton and Rose's test. When she resumed her usual activities, she began to complain again of precordial pain, which was brought on with exercise. The pain radiated to the back and to the left arm and disappeared either with rest or with nitroglycerin. Later, the pain began to appear even at rest and was brought on by small efforts, especially after a meal. She was treated with papaverine, triethanolamine trinitrate biphosphate, pentaerythritol tetranitrate, propylthiouracil, aminophylline, heparin, a low salt diet, and rest. The effort of climbing on to the exploration table was sufficient to produce pain and an electrocardiogram similar to what might be expected with an exercise test. Three days after administration of Marsilid was begun the pains diminished, and after eight days she had no precordial pain. Her capacity to walk increased to the point where pain did not appear, even after she walked several blocks. She complained of headache, which she ascribed to Marsilid. She stopped the medication and the headache disappeared; eight days later, she again had some precordial pain.

Effect on Resting Electrocardiogram. We have observed in many patients that the ST segment returns to normal and that negative T waves become positive. This occurred in 1 patient after seven years of abnormal electrocardiographic findings.

Case 2. A 57-year-old man, seven years earlier had had an acute attack of coronary thrombosis, with severe pain in the chest radiating to the back, left arm, and shoulder, sweating, and hypotension. The patient had a history of hypertension (190/110 mm. Hg.), which was known by him for over four years. He was kept in bed eight weeks and slowly resumed his activities. His blood pressure went up again to its previous figures, and the patient began complaining of chest pain, both after effort and at rest. From 1950 to September 1957, he was treated with all known vasodilators, thyroid-blocking agents (with the exception of I^{131}), heparin, anticoagulants for long periods, and hypotensive drugs (with the exception of methonium salts or pentapirrilidinium). Four days after administration of Marsilid was begun, the pains began to diminish, and on the twelfth day the attacks disappeared. His capacity for effort became normal. Before treatment, he was taking an average of 25 nitroglycerin tablets every two days. Since the twelfth day of Marsilid therapy, he has taken no nitroglycerin, although he carries them in his pocket. His blood pressure fell to 170/90 mm. Hg.

SIDE EFFECTS

Gastrointestinal. Fourteen patients reported constipation and/or flatulence. Diarrhea occurred in 1 patient. Twenty-three patients complained of dryness of the mouth.

Urinary. Nine men reported difficulty in starting micturition. Two of them, without consulting us, consulted a urologist; 1 of them underwent cystoscopy under anesthesia, and a transurethral resection was performed. As no previous prostatic examination was done in any of the patients, we cannot report if the patients who had difficulty initiating micturition had benign prostatic hypertrophy or not.

Locomotive. Eighteen patients complained of pain in the legs, fatigue, or both, especially after walking a distance to which they were not accustomed. It is interesting to report that 7 of the patients with severe arteriosclerosis, who had intermittent claudication before treatment, showed improvement of this symptom.

Psychic. Some patients reported a sense of well-being. Some were frankly euphoric, 3 to the point of mania. Other patients reported somnolence during the first week of treatment.

Central Nervous System. Two of the patients complained of slight headache, 3 of severe vertigo, and 6 of light vertigo.

Blood Changes. In the 12 patients studied, no changes were observed in the blood picture. One of the patients had leukemia, with a red blood cell count of 1,800,000 and a hemoglobin of 7.4 Gm. The anginal pains, which were frequent and severe, also disappeared in this case, and the patient required nitroglycerin only occasionally. After transfusions, even this occasional need was avoided. This patient had suffered from angina for eight years before leukemia became apparent, aggravating his symptoms until Marsilid therapy was initiated.

Hypotensive. As time goes by, the hypotensive action of Marsilid, especially orthostatic, has become more apparent as a cumulative effect. Although this action will be reported later with an analysis of our cases, we can say the following. (1) Marsilid has a very important hypotensive effect. (2) This effect is slow to appear, which would suggest that it acts either through a metabolite or a substance produced in the body by Marsilid. (3) The effect is more apparent orthostatically, as in persons having undergone sympathectomy. (4) The modification of the blood pressure figures is important and sometimes it is lowered to the point of collapse. (5) The effect has been noticed, not only in persons with high blood pressure, but also in normotensive persons. (6) The effect is long-lasting, up to four weeks in 1 case, after withdrawal of Marsilid.

COMMENTS

We have in Marsilid a medication that has an undoubted beneficial effect on anginal pain and on its relation to effort. It acts by abolishing the pains and improving the capacity for effort. This is an unusual finding in a disease in which all previous treatments, medical or surgical, had been of doubtful or limited value.[7–9]

Marsilid proved to be a fast acting drug, since the total response was noted within the first week in most of the patients, and in no case later than the twelfth day. According to reports in the medical literature, its stimulating effect on psychic depression appears between

one and four weeks or more of treatment.[10–13] Some of our colleagues have suggested the possibility that our results might be due to a change of the patient's attitude toward pain. This seems to us most unlikely.

Throughout the study an empirical dose of 150 mg./day was prescribed to all the patients, but we now think that we are very near the minimal useful dose, as a recurrence of symptoms ensued when the dose was reduced to 75 mg./day. In any case, this dosage is well below the therapeutic dosage administered to patients with tuberculosis.

In most of the studies evaluating the therapeutic worth of medical or surgical measures in the treatment of angina pectoris, variation in the daily intake of nitroglycerin has been taken as a useful guide to the effectiveness of such measures; generally, a statistically significant reduction in nitroglycerin intake has to take place in order to prove the efficacy of a given method. In the 72 cases studied by us, the patients were taking, before treatment, not less than 4 nitroglycerin tablets a day (some of them up to 30 tablets daily), with an average of 9 tablets/day. After the total response was achieved with Marsilid, we recorded a total intake of only 47 nitroglycerin tablets in our 72 patients during the entire time of the study.

It is still too early to attempt to draw any conclusions on blood levels or the duration of action, as further studies are to be made. There is evidence that all Marsilid disappears from the blood after thirty-six hours, but we have no definite studies on tissue concentrations.

In relation to the electrocardiographic changes, we should like to say that in our opinion, as in that of most authors,[7, 14–19] angina pectoris is a disease that should be diagnosed mainly by clinical history, very little data being obtained from physical examination and laboratory tests. The electrocardiogram is the best auxiliary method for differential diagnosis in doubtful cases and, with all its shortcomings, it is the best objective index of coronary disease. This is the reason we placed special emphasis on studying the electrocardiogram, and we found that in many patients the subjective improvement coincided with the improvement noted on the electrocardiograms, not only in relation to the exercise test, which gave negative results in all the cases after total response had been reached, but also in the resting electrocardiogram, in which normalization of T waves that suggested ischemia would seem to indicate that the action of Marsilid is not only symptomatic, but that it has a direct action on the pathogenesis of angina pectoris. More needs to be written on these electrocardiographic changes, but we think that what we have seen until now is most unusual. The side effects that we have found and that have been reported in the literature are of minor importance, although we think that, with prolongation of treatment, they will warrant further investigation. We do not know how long we will be able to keep the patients under treatment, nor do we know if the action of the drug will wane. We do not know if, with prolongation of treatment, we will be able to reduce or stop the dosage, or if, on the contrary, we will have to increase it in order to maintain the beneficial effects. We do not know if prolonged administration will produce toxic manifestations or whether such changes are reversible. We know of 1 case of liver damage and 2 cases of reversible amaurosis.[20] We have not observed this in our own series. As we state in our results, constipation and flatulence were fairly constant findings that were controlled with light laxatives. One of the

patients stopped taking Marsilid because of constipation, but when the anginal pains returned, he decided to resume taking Marsilid, stating: "I prefer to be constipated and take laxatives, than to have my pains and need nitroglycerin." The effects on the urinary system were more annoying, although less frequent. Yet, in 1 case already reported, a transurethral resection was performed because the patient and his urologist were not aware that the effect was due to Marsilid. Consequently, patients must be told about this side effect and advised to report it, to avoid repetition of this mistake.

In relation to the side effects associated with walking, a large percentage of the patients complained of pain and fatigue in the legs, and, although this effect has not been reported in the papers dealing with Marsilid in tuberculosis[21–24] or as a stimulant, it is a finding that merits further investigation. It could be due to the fact that our patients are not used to the physical efforts they are now performing. Although we have given our patients a fairly free hand in their physical activities, we have definitely advised them not to overdo; however, some of them, under the influence of the euphoria produced either by the central action or by the absence of the pains, feel a compulsion to be active. We have found this need for activity a most difficult problem to handle, as we have no way of measuring the amount of physical activity that our patients should be permitted following the disappearance of pain, which was the limiting factor.

A most important point to discuss, which we are as yet reluctant to do, is the mechanism of action.[3, 25–30] We know that Marsilid is a potent inhibitor of aminoxidase, and therefore modifies the concentration of serotonin. If these substances play any role in angina pectoris, it is not known, and we have found no report in the medical literature that this point has been studied. However, from the theoretical point of view, and from what we do know about the action of Marsilid on aminoxidase and serotonin, its effects could be far from beneficial.[31] On the other hand, adrenergic blockade and catecholamine inactivation by Marsilid have been reported, an action that, in the opinion of several authors,[32] could be beneficial.

We have no evidence that Marsilid acts as a vasodilator, and we have some evidence that it does not act as an analgesic. Intermittent claudication was not benefited by the drug.

Therefore, we think that the mode of action can be found in the study of the action of Marsilid on myocardial metabolism, a study that may give a clue to the effects that we have reported and also open the door to a different approach to the study of angina pectoris, with coronary flow as a secondary factor and with myocardial demands and metabolism as the primary factor.

CONCLUSIONS

1. Administration of Marsilid relieves the anginal syndrome, abolishing pain and increasing the capacity for effort.
2. A daily fractionated dose of 150 mg. proved to be useful in all patients treated.
3. The initial response was observed on the third day; total response occurred from the fourth day.
4. Suspension of Marsilid therapy caused recurrence of the symptoms between the third and eighth days; remission of pain occurred upon readministration of the drug.
5. Diminution of the dose to 75 mg./day proved ineffective to control the syndrome.

This would seem to indicate that the dosage empirically used throughout our study is very close to the minimal useful dose.

6. The Master two step tolerance test gave negative results in all patients after total response was achieved, even when positive results were obtained before treatment.

7. Similarly, the abnormal, pretreatment resting electrocardiogram proved to be favorably modified by Marsilid.

8. Long term (up to five months) administration of Marsilid at these doses apparently produced no important toxic effects. Side effects were noted on gastrointestinal function (constipation, flatulence); the urinary system (delay in initiating micturition); locomotive system (fatigue, weakness, and paresthesias in lower extremities); and on the central nervous system (euphoria, somnolence, and vertigo). Side effects may prove to be the limiting factor in the usefulness of the drug.

9. In relation to Marsilid's mode of action, it is suggested that it probably acts directly on cardiac metabolic and enzymatic processes by modifying their demands, and not as a vasodilating or analgesic agent.

10. Together with its empirical but undoubtfully useful therapeutic value, it is thought that Marsilid also will prove to be of importance in the reinvestigation, re-evaluation, and widening of our present concepts of the pathophysiology of angina pectoris.

SUMMARY

The action of Marsilid on angina pectoris was studied in 72 patients with severe cases. In all of them remission of symptoms was obtained. This was coincident with improvement in the electrocardiographic findings both after the exercise test and in resting tracings.

It is concluded that Marsilid is a specific and new form of treatment in angina pectoris, and that elucidation of its pharmacodynamics will shed important light on the pathophysiology of the syndrome.

ADDENDUM

After this article was written we received the final data on 1 patient with severe aortic insufficiency who had had anginal pains for three years, especially at night, and who had received no benefit from surgical revascularization. This patient took an average of 5 to 6 nitroglycerin tablets per day. After four days of Marsilid therapy, the pains diminished greatly in intensity, and pressure was the only complaint. After the seventh day, even this disappeared. Follow-up four months later indicated that the patient has had no pain or pressure whatsoever, and has not needed nitroglycerin.

RESUME

L'auteur a administré le Marsilid à des malades déprimés atteints d'angor pectoris. A la grande surprise de l'investigateur, le malade a signalé une réduction du nombre des crises angineuses au bout de cinq jours de traitement. Trois jours plus tard, les symptômes avaient

complètement disparus. Les résultats obtenus chez ce malade paraissent particulièrement significatifs car les manifestation angineuses existaient depuis longtemps.

L'auteur a alors administré le Marsilid à un groupe de 72 patients présentant une forme sévère d'angor pectoris avec douleur au moindre effort et en décubitus. La réaction initiale au traitement par le Marsilid, rémission des symptômes, abolition de la douleur et augmentation de la capacité de supporter l'effort, se sont manifestées en trois à dix jours. Le besoin de trinitrine a graduellement diminué.

On a décelé des effets secondaires à l'égard de la fonction gastro-intestinale (constipation, flatulence), de la fonction urinaire (délai du début de la miction), du système locomoteur (fatigue, asthénie et paresthésies des membres inférieurs) et du système nerveux central (euphorie, somnolence, vertige).

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Toxicology of Marsilid*

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The pharmacology of Marsilid‡ is characterized primarily by its effects in elevating the concentration of biological amines in tissues and in modifying the action of numerous drugs. Classic pharmacologic methods gave no insight into the mechanism of action of Marsilid.[1] Studies in chemical pharmacology gave the first fundamental clue; Zeller and Barsky[2] discovered that Marsilid is a potent inhibitor of amine oxidase. The enzyme was inhibited in brain and liver when Marsilid was injected into animals.[3] The function of this enzyme is the removal of biological amines from the body and the prevention of accumulation of these amines in excessive amounts. Marsilid, the inhibitor of amine oxidase, can cause the accumulation of serotonin[4] and norepinephrine[5] in a manner analogous to that in which neostigmine, the inhibitor of cholinesterase, causes accumulation of acetylcholine. The potentiation of the action of tyramine and phenethylamine by Marsilid was demonstrated by the prolongation of their action on the response of the nictitating membrane in the cat.[6, 7] The toxicity of amines such as tyramine and phenethylamine, which are destroyed by amine oxidase, was increased by Marsilid in guinea pigs, but the toxicity of ephedrine and of phenylisopropyl amine, which are not destroyed by amine oxidase, was not affected.[8] Therefore, the modification of the action of other drugs is a characteristic pharmacologic property of Marsilid.

A second clue to the pharmacologic action of Marsilid was the discovery by Fouts and Brodie[9] that Marsilid inhibits the enzymes in the liver, whose function it is to detoxify various drugs. First they confirmed the observation of Goldin *et al*[10] that Marsilid potentiates the action of barbiturates in mice, although Marsilid alone has no sedative effect. They demonstrated that hexobarbital hypnosis was prolonged because Marsilid inhibited the enzymes in liver microsomes, which destroy the barbiturate. In like manner they found that Marsilid inhibits the rate of destruction of amphetamine, aminopyrine, and acetanilid. Such studies explain the Marsilid potentiation of the action of many drugs, which are ordinarily destroyed in the liver. This action on liver enzymes could account not only for the activity but also for part of the toxicity of Marsilid.

Chemistry. The generic name of Marsilid is iproniazid, which was derived from the chemical name, 1-isonicotinyl-2-isopropyl hydrazine. It is a white, crystalline material that is soluble in water as the base or as various salts.

Classic Pharmacology. The chief characteristic of Marsilid in classic pharmacologic tests is its inertness.[1] It has a very low order of activity in acute tests for blood pressure effects in various species. It does not affect the response of the blood pressure to acetylcholine,

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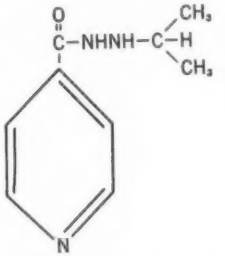
‡ Marsilid is the trade name of Hoffmann-La Roche, Inc. for iproniazid.

serotonin, carotid occlusion, or vagus stimulation. It has no blocking effects on ganglionic transmission or on neuromuscular transmission. It has no significant effect on the seminal vesicles, the bronchioles, or the intestines, either intact or *in vitro*. It does not seriously affect the responses of smooth muscle of intestine to barium, histamine, or acetylcholine. It does not suppress secretions such as salivation in rabbits, or lacrimation in rats. It does not have mydriatic or local anesthetic action on rabbit eyes.



Amine Oxidase Inhibition. In mice, a single large dose of Marsilid reduced the amine oxidase activity of the brain for five days,[3] and the reversal of reserpine sedation could be demonstrated for up to three weeks.[11] We have confirmed these observations in rats.

The data in table I demonstrate the long duration of the amine oxidase inhibition in the rat brain and the equally long duration of the blocking effect on reserpine ptosis in rats. These effects were measurable in the rat for twenty-five days after a single dose of Marsilid.

Acute Toxicity. Marsilid has very low acute toxicity in various species. The toxicity is nearly the same by various routes, indicating nearly complete and rapid absorption from various sites. The LD_{50} in mice varies from 615 to 950 mg./Kg. by various routes.[1] Convulsions occurred at the lethal dose. Oral LD_{50} in rats was 383 mg./Kg. and in rabbits 125 mg./Kg. Convulsions also occurred in these species.

Subacute Toxicity. The results in table II show that Marsilid is much more toxic when given repeatedly over several days than it is after single injections. In all species there is evidence of cumulative toxicity. The tolerated doses are 10 mg./Kg. orally in rats, rabbits, cats, and dogs for short periods of one to four weeks. Larger doses and more prolonged treatment cause loss of appetite and loss of weight as the first symptoms. Persistent treatment with large doses leads to death. The cumulative effects of Marsilid are partially explained by the irreversible nature of the amine oxidase inhibition.

Chronic Toxicity. When Marsilid was mixed in with food and fed to immature rats for thirteen weeks at concentrations of 5, 20, and 80 mg./Kg., there was no effect upon survival of the animals.[1] Growth was slightly retarded. A moderate decline in hemoglobin, hematocrit, red cell count, and white cell count was noted at the two highest dose levels. Microscopic studies of the tissues of these animals on higher doses showed increased destruction of red blood cells, engorgement of the spleen, and bone marrow hyperplasia.[12] There was slight parenchymatous degeneration in the liver and the kidney with the high doses.

Dogs were given Marsilid at doses of 3.5, 7.0, and 14.0 mg./Kg. by oral, intravenous, and

TABLE I

*Effects of Marsilid in Rats**

Time	Amine Oxidase Inhibition in Brain (%)	Response of Ptosis to Reserpine
2 hours	79	Blocked
4 hours	89	Blocked
8 hours	87	Blocked
24 hours	81	Blocked
2 days	71	Blocked
3 days	65	Blocked
4 days	62	Blocked
5 days	68	Blocked
10 days	52	Blocked
15 days	39	Blocked
20 days	31	Blocked
25 days	21	Blocked

* Dose, 50 mg./Kg., orally.

TABLE II

*Subacute Toxicity**

Species	Dose (mg./Kg.)	Duration (weeks)	Effect
Rat	10	5	None
	40	5	Weight loss
	200	5	Kidney and spleen enlarged and dark
Rabbit	10	2	Loss of weight
	25	2	Death
	50	2	Death
Dog	5	4	Normal weight
	10	4	Normal weight
	20	4	Loss of weight and appetite; death
	25	1	All died
Cat	10	1	No effect
	25	1	Loss of weight; death
	50	1	Death
Guinea pig	40	2	Tolerated

* Oral route.

intramuscular routes for thirteen weeks.[1] All dogs survived the treatment, and no effects on weight were observed. No change in the blood picture was evident when 3.5 mg./Kg. were given. There was a slight reduction in red blood cells, hemoglobin, and hematocrit at 7 mg./Kg. and more significant reduction at 14 mg./Kg. At autopsy slight alterations in spleen, bone marrow, and liver were noticed in the animals who had received 3.5 mg./Kg. Moderate changes were observed at 7 mg./Kg. in these organs, and marked changes were found at the 14 mg./Kg. dose level. The livers were pale brown, the kidneys presented fibrosis, and the spleens were enlarged, dark, and firm. The bone marrow was hemorrhagic.

Microscopic examinations[12] revealed deposits of blood pigment in the livers and moderate toxic effects in the kidneys. These changes were believed to be reversible, since 2 dogs, sacrificed two weeks after termination of the Marsilid administration, showed little abnormality in the tissues.

Metabolism. The plasma levels of 6 human subjects after oral administration of doses ranging from 1.5 to 3.2 mg./Kg. reached maximum levels of 0.15 to 0.7 mg. per cent in two hours, with a return to zero in twenty-four hours.[13] De Ritter et al[14] studied the excretion of Marsilid in 9 human subjects after oral administration of 250 mg. About 12 per cent of the administered dose was excreted in twenty-four hours, and only slightly more in the next twenty-four hours. Isonicotinic acid, the split product of Marsilid, was excreted in large amounts. About 40 per cent of the Marsilid dose was excreted as isonicotinic acid in twenty-four hours and 50 per cent in forty-eight hours. About 62 per cent of the total dose of Marsilid administered was thus accounted for in the urine in forty-eight hours. The method employed for the determinations involved measuring the isonicotinic acid by the cyanogen bromide idometric method. Marsilid was measured by the same method after hydrolysis. This method does not account for the hydrazine portion of the Marsilid molecule.

The rapid excretion of the isonicotinic acid moiety of the Marsilid molecule indicates rapid splitting of Marsilid. However, Marsilid has a long duration of action as an amine oxidase inhibitor. A single dose produces effects for at least three weeks in rats. Therefore, it would appear that the hydrazine moiety of the Marsilid, which has not been accounted for in urinary studies, probably remains attached to the amine oxidase. This attachment appears to be very strong and is perhaps irreversible. The results indicate, therefore, that isopropyl hydrazine is the active moiety of the molecule, whereas the isonicotinic acid group is the carrier.

SUMMARY

Marsilid has low toxicity when given in single doses but shows cumulative toxicity on repeated administration. This is partly related to the irreversible nature of the amine oxidase inhibition and perhaps of the inhibition of detoxifying enzymes. The toxicity in animals may be related to the hemolytic properties of the hydrazine moiety with resultant accumulation of split products in tissues. Prolonged administration of toxic doses leads to loss of appetite, loss of weight, anemia, and deposit of blood pigment in the liver. The toxicity is reversible at moderate dose levels.

RESUME

Les effets toxiques du Marsilid sont réduits quand la drogue est administrée à dose unique, mais il se produit un effet toxique d'accumulation par le répétition de l'administration. Cet effet est partiellement en relation avec la nature irréversible de l'inhibition de l'amine-oxydase et, éventuellement, à l'inhibition des enzymes de détoxication. Chez l'animal, la toxicité a été rapportée aux propriétés hémolytiques de la fraction hydrazine entraînant l'accumulation de substances dédoublées dans l'organisme. L'administration prolongée de doses toxiques détermine la perte de l'appétit et du poids, l'anémie et le dépot de pigments sanguins dans le foie. La toxicité est réversible lorsque des doses modérées sont administrées.

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The Present and Future of Marsilid

Open Discussion

CHAIRMAN ELMER SEVERINGHAUS:* It is always hazardous to assume that one can explain all the activities of a given chemical compound in terms of one biochemical or one pharmacodynamic activity. I am going to suggest that it might be wise, in line with the general laws of scientific parsimony, to have a working assumption that Marsilid has one fundamental action, namely, as an antimonoamine oxidase; to recognize that there may be a wide variety of pictures seen in different patients, on different dosages, with different methods of administration, because we would have to keep in mind the fact that this antimonoamine oxidase would be effective in the brain, in the blood platelets, in the bowel, and even in the heart, as sites of action. We will have to discuss the differences dependent on the rate of penetration into these different tissues, and the distribution in the intracellular and the extracellular fluids. We will have to think about the permanence of Marsilid in contact with tissue and about the possibilities that a metabolic transformation product from Marsilid may turn out to be either the active or an inactive agent, and that the duration of effect will be another parameter of our results.

With this hypothetical digression, I am going to turn the matter over to our panel.

DR. KLINE: In my paper, I indicated that I believed it entirely conceivable that there may be pharmaceuticals capable of extending so-called normal behavior. Marsilid is one of the pioneers in this area. Common to all of these is an increase of energy.

Sleeping, for instance, is an unexplained phenomenon. There is really no evidence that anyone has adduced to show that this is an essential function. It might be possible to find a drug, such as Marsilid, that would enable people to get along with less sleep. There are a variety of other functions that we certainly could improve.

It appears possible that Marsilid may be of value in physiologic as well as psychological conditions by increasing anabolic processes.

A particular situation that I should like to touch on is the effect of Marsilid in multiple sclerosis. A few patients with multiple sclerosis experienced exacerbations of their disease when this drug was given. If we find that this is actually the case, it may provide a substantial lead in the search for the causes of this disease.

I would reaffirm the need to understand that there are important areas of information and investigation common to both psychology and physiology and that there is no incompatibility between these disciplines.

DR. GOLDMAN: Dr. Kline has said many things touching on areas in which I have been interested.

New concepts have been developing since the advent of drug therapy in gross psychotic manifestations, supposedly of purely psychogenic origin, such as old-fashioned dementia praecox or the middle-fashioned schizophrenia.

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It is obvious to those of us who are dealing with schizophrenic patients that we are dealing with a disorder in perception at the level of concept formation, in which the material, coming in from a sensory inflow, is not being related to the world as it exists but to an internal world of the schizophrenic. It is a world made up of fears, prejudices, and distortions of reality. When we give useful, adequate drugs, such as the better phenothiazines, to patients who have not been sick so long that the patterns are fixed, these distortions disappear, and the patients relate again to reality as it exists. The delusions cease to be delusions, and the patients sometimes come up with amazing explanations, keener than any of the psychological concepts that have been developed by the cleverest psychologically oriented physicians.

There is a group composed of patients who have been singularly resistant to any change with the application of the phenothiazines. These are the depressed patients, the very patients who have been particularly influenced by the administration of Marsilid.

It is important for us to understand the chemical mechanisms involved if we are to pursue our goals more vigorously. We have made another contribution to the development of the organic theory as an explanation of the distortions of performance and thinking that we term psychosis or, perhaps, even of those that constitute psychoneurosis.

There is another aspect to be considered, and that is the value of Marsilid in treating, and in gaining greater understanding of, those somatic disorders, such as angina pectoris and colitis, that have a strong psychological component.

CHAIRMAN SEVERINGHAUS: Now I am going to ask Dr. Zeller to take over on the somatic side, and tell us what he has in mind for the future.

DR. ZELLER: I am responsible for two things on the title page of our program: the name "monoamine oxidase" and the idea that Marsilid could act by blocking monoamine oxidase.

This finding has helped to get Marsilid off the shelf and has aided tremendously in our enzymologic studies involving the reactive surface of enzymes. The analysis of the metabolism of serotonin, norephinephrine, and other compounds was of great help in pharmacologic work and even, ultimately, in reintroducing the drug clinically.

It is important that we remain open-minded. We have shown that histamine and methylated histamines, which occur in metabolism, are also substrates of monoamine oxidase. Therefore, we should also look in the direction of histamine and histamine metabolism as a possible part of the explanation of the action of Marsilid. In this connection, of course, the question of the role of histamine in the production of postural hypotension is raised.

It has been suggested that many other effects may be produced by Marsilid, and in this I concur. We may not even know the real targets of this drug nor the enzymes involved, so we should remain as cautious as possible.

For the future in this work, I should like to point to the following situation: It has taken us several years to analyze the mode of action of Marsilid on one or two enzymes, and we used hundreds of compounds to get to the bottom of things. We think we can see the end in sight, but, even so, a lot of work still has to be done.

The same intensity is also necessary for the study of this problem. How long does such a drug stay within the cell or in the particulate matter of the cell? What happens to it?

What products are formed? How long do they stay around? And, again, what is the influence of the over-all structure or the individual parts on such problems as maintenance, metabolism, or excretion of these compounds?

There is much to know, and much basic work still has to be done in regard to the question of the diagnosis of the endogenous psychoses. For example, we may be able in the future to determine that certain metabolic disorders occur in one form of schizophrenia and other metabolic disorders in a second form, and so that we do not need to rely on clinical analysis alone but can depend, in part, on laboratory findings for a more exact diagnosis.

I believe that, in this respect, Marsilid already has been of great help, because we now have a way to change certain metabolic patterns. I think that this is one of the contributions that might become more important than others.

We are all aware that Marsilid is wonderful material to start with, but I am sure we are all convinced that it will not be the last word; it is the beginning of a line that, we hope, will go very far. We should get as much solid, precise information about the mode of action of this most interesting substance as a basis for the development of new drugs, so that we lend more dignity to the therapy, and treat diseases more systematically.

CHAIRMAN SEVERINGHAUS: I am sure that you all agree with me that we are very fortunate to have Dr. Zeller with us in this discussion. His first contribution in this particular program was identifying Marsilid as an inhibitor of monoamine oxidase; he has persisted in this study, and is working in clinical areas as well as with fundamentals. Speaking for Hoffmann-La Roche, we share with Dr. Zeller the expectation that this will only lead us to more compounds that will have both the analogous and different effects that we require.

Dr. Udenfriend, you and your associates at the National Institutes of Health have had extensive experience in studying the biochemistry and pharmacology associated with this field of Marsilid action, and we shall be glad to have your comments about what is around the corner.

DR. UDENFRIEND: I think it is a reflection of the times that compounds of this sort are discovered by psychiatrists. The psychiatrists happen to be on their toes, as far as the biochemical, chemical, or pharmacologic advances are concerned. Twenty years earlier, it might very well have been a cardiologist who would have picked up this compound as a useful drug.

I think that, given a drug that influences sensitive and selective enzyme systems found primarily in the central nervous system but also present in other tissues, its use is going to produce psychotic effects or influence the behavior of patients. However, one may have to point out that the particular enzyme systems involved may be responsible for very definite functions having nothing to do with behavior or with the behavioral patterns, that come to the attention of a psychiatrist. They may probably be involved in the general functions of the body. A compound like Marsilid has some very far reaching effects. Many of the effects that have been observed may not be direct actions on a site, such as the heart, wounds, or the skin, but central actions are transmitted as are endocrine functions or through some endocrine system in the body.

In dealing with the chemical or the chemicopharmacologic aspects, we ought to divide the

discussion into two parts (actually, more than two parts, but these two to begin with). One concerns Marsilid itself, and the other relates to the amines and the enzymes involved in their metabolism, the monoamine oxidases.

Marsilid, in addition to being a useful drug, is also a most useful tool in understanding some enzymatic reactions and some physiologic reactions *in vitro* and *in vivo*.

Another useful function that Marsilid has been able to serve is that it has made it possible to uncover other routes of metabolism of these amines and also to point to other mechanisms that we may have to deal with pharmacologically in order to potentiate these amines. The two are now quite apparent. If one pretreats animals with Marsilid, peripherally injected serotonin is metabolized to the same extent as in untreated animals. Although the effects are potentiated one asks oneself how much more fully potentiated these effects would be if one could block the destruction completely. It now turns out that there is another alternate route that is active peripherally. Can we block this route as well, and what would be the consequences?

The same thing has come up from the standpoint of the catecholamines, adrenalin, and noradrenalin. More recently, Dr. Carlson and others have found DOPA-amine in the heart and in the brain. This is another amine to be considered. Here, again, it appears that Marsilid does not block the metabolism, at least does not block it effectively, and one of the alternate routes that have been put forward so well by Dr. Axelrod may be considered. What would happen if we were to block this route of metabolism? Maybe we would obtain even more astounding results. I think that this is important because the effects produced by the administration of Marsilid itself, in amounts that are known to produce almost complete block of monoamine oxidase, are not as astounding as we would think they should be were they completely blocking amine metabolism.

The other point, I think, that one should make relates to the structure of this monoamine oxidase inhibitor. A great deal has been said about the relationship of a hydrazine type of structure to monoamine oxidase inhibition, and I know what Dr. Zeller has in mind; that, in this particular series, it is important. But, I think, it should be pointed out to some who may not be aware of it that if one goes to the shelf of a chemical laboratory and pulls compounds off at random, one out of three will be fairly good monoamine oxidase inhibitors *in vitro*, and in fact one can find a large percentage in a study, as we have done, that will all be fairly active *in vivo*, and compare favorably with Marsilid *in vitro*. But there have been found, and there are being found, inhibitors that are as potent as Marsilid *in vitro*, or even more potent; that are reversible, and that have structures that are completely unrelated to hydrazine. I think the significance of this is that, if Marsilid is acting through monoamine oxidase, it becomes important to compare its side effects with these other compounds.

The final point I should like to make is that another factor should be considered in dealing with what is a foreign compound. This is something that Dr. Zeller mentioned: that the compound may be acting in a manner totally unrelated to its antimonoamine oxidase action.

CHAIRMAN SEVERINGHAUS: We have had a most interesting program. I say again that we appreciate your having shared your wisdom and experience with us.